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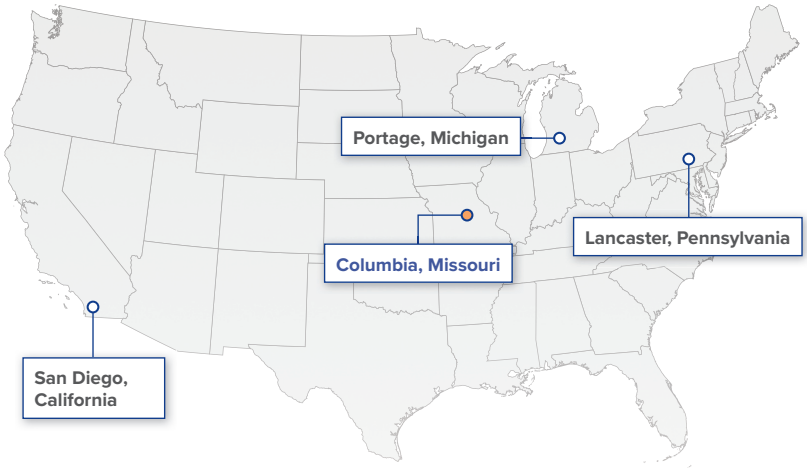

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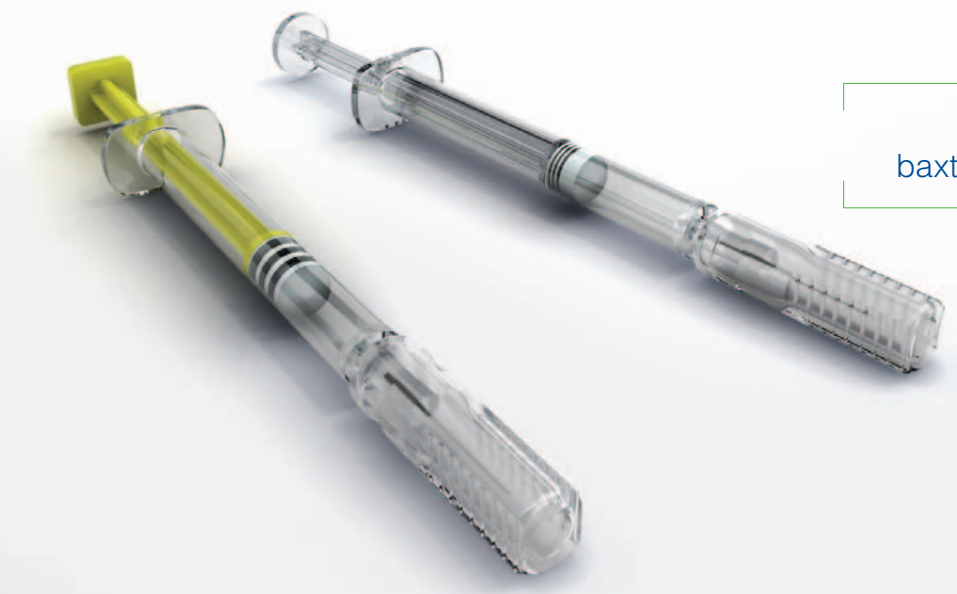

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What Ifs in the Five-Year Plan

Jim Miller

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Heightened uncertainty means CDMO executives need to play out planning scenarios.

Long-term strategic planning must always contend with uncertainty about future business conditions, but the current bio/pharmaceutical industry environment makes forward planning especially difficult. Macro-economic conditions are changing; long-established business practices are being disrupted; and political instability is widespread. It is increasingly difficult to have confidence in one's assumptions about the context in which any industry must operate.

In such a volatile environment, contract development and manufacturing organization (CDMO) executives must test how their strategies will hold up in the event that long-held assumptions about the external environment are upset by new realities. They need to play out "what-if" scenarios that test the robustness and appropriateness of their strategic initiatives and investment plans in the event actual business conditions diverge from their expectations.

Here are five what-if developments that CDMO executives need to consider carefully as they prepare and implement their business plans.

What if payers in the US crackdown on drug prices?

Expenditures on drugs account for just 10% of all healthcare expenditures in the United States, but they draw inordinate attention because consumers must pay a significant portion of drug costs out-of-pocket.

CDMO executives need to consider multiple scenarios if US drug prices are attacked by government and private payers. Bio/pharmaceutical companies could respond by insisting on better pricing from their suppliers, including CDMOs, and by bringing contract manufactured products back in-house to absorb more fixed manufacturing overhead. Alternatively, they could decide to pare down their manufacturing networks and reduce capital expenditures, which could be a boon for CDMOs.

The greatest and most negative implications are likely to be for R&D spending. Companies that self-finance R&D spending will likely reduce costs by shrinking the number of candidates they have in their pipelines.

Jim Miller is founder and former president of PharmSource, a Global Data Company.

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For emerging bio/pharma companies that depend on CDMOs, the impact would be more severe. Lower or uncertain drug prices would reduce valuations of in-licensed and acquired drug candidates, and the emerging bio/pharma companies that develop them. That would reduce the flow of external funds available for their R&D activities, most of which get spent with discovery and clinical contract research organizations (CROs) and CDMOs.

The uncertainty surrounding international trade should be a matter of great concern for CDMO executives.

What if funding for emerging biopharma slows down?

There is now a symbiotic relationship between CDMOs and emerging bio/pharma companies: because there is a robust CDMO sector to serve the development needs of emerging bio/pharma companies, those companies can be set up on a virtual model that requires much less financing than if they had to invest in their development infrastructure. That means that the fortunes of CDMOs are now tied closely to emerging bio/pharma's access to external financing. That financing has historically been cyclical, and the industry has benefited from the current, historically-long run of funding availability. When the cycle dips down again, as it did in 2007, the consequences could be devastating for the CDMO industry: a number of CDMOs may go out of business and others may have to impose deep staff cuts and postpone capital investments to ride out the downturn.

CDMO executives preparing for this eventuality will need to be aware of several factors. One is the nature of their offerings: CDMOs dependent on early development projects, which tend to have short timeframes, will feel a slowdown more quickly than CDMOs that have a strong mix of Phase II and III projects. Secondly, they should monitor the financial health of their major clients to determine if they have sufficient cash on hand to complete the program they are working on. Finally, CDMO executives will want to keep a close eye on their company's spending, which can get out of hand when the business is growing rapidly.

What if trade in pharmaceuticals becomes a victim of the trade war?

The uncertainty surrounding international trade should be a matter of great concern for CDMO executives. Bio/pharmaceutical ingredients and products are among the most actively traded goods in the global economy.

Responding to the imposition of tariffs and non-tariff barriers would be difficult for the bio/pharmaceutical industry, whose supply chains are particularly inflexible. In the best of circumstances (i.e., when spare capacity is readily available), it takes several years to qualify new production sites. But spare capacity is not readily available, especially for small- and large-molecule APIs and injectable drug products, and especially in the US. So if bio/pharmaceuticals get caught up in a trade war, costs will likely increase to reflect tariffs and bio/pharma companies will expect their CDMOs to absorb some of the higher costs.

Longer term, bio/pharma companies could redesign their supply chains to localize more production, giving up economies of scale to avoid the tariffs. That could be favorable to CDMOs as contract manufacturing for a particular market could be more cost effective than building a captive facility. But companies would have to believe that the restricted trade environment was a fixture before undertaking the massive capital expenditures and effort that such a redesign would require. Bio/pharma and CDMO executives would likely be reluctant to move ahead with such a plan given the risk and uncertainty it would entail.

What if new processing technologies become widely adopted?

CDMOs have generally been followers in adoption of new technology as they lack the resources available to global bio/pharma companies to do technology R&D. As bio/pharma companies develop products incorporating new technologies such as continuous manufacturing, CDMOs will have to figure out how to underwrite the capital expenditure and develop the expertise to implement them. This is likely to require skills in partnering with clients to co-develop and co-invest in the technologies. It is also likely to favor financially-sound CDMOs that can provide assurance that they can be reliable long-term partners in innovation.

What if industry restructuring dumps capacity into the CDMO space?

Large global bio/pharmaceutical companies of all stripes are restructuring their manufacturing networks and supply chains. The CDMO industry has gained most of its capacity as a result of plant divestitures by large bio/pharma companies, but the result has been a large amount of undifferentiated available capacity and a number of CDMOs facing financial difficulties, especially in Europe.

CDMO executives must consider the implications of a large amount of new bio/pharma capacity coming into the market on top of the capacity that CDMOs are investing in themselves. A market already awash in capacity for low-value solid and liquid dose forms is likely to be pressured as more capacity becomes available. There are still investors new to the industry that are looking for a way into the CDMO market, and political pressures to maintain marginal facilities remain high. Even a small amount of incremental capacity from bio/pharma companies could severely impact profit margins and cause the contract services industry a lot of pain. **PT**

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Designing Combination Products

Andrew Gaillard and Mark Gordon

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API can be mixed with silicone and other polymers to create drug-delivery combination products. This article presents some examples of combination devices being tested or currently in use along with factors for consideration when developing them.

Andrew Gaillard is global director, and **Mark Gordon** is product manager, both at Trelleborg Sealing Solutions Healthcare and Medical.

Silicone has long been a favorite material of medical product designers who value its stability, physical properties, and biocompatibility. For these reasons, medical grade silicones are commonly used across a wide variety of medical devices and drug delivery products.

In addition to the physical properties that make silicone a preferred material for medical devices, its chemistry and cross-linking characteristics make it an ideal material to use in many drug delivery applications. Combination products include combinations of two or more of these three components: medical devices, drug, and biologics. For this article, the combination of a medical device and active pharmaceutical ingredient (API) will be considered.

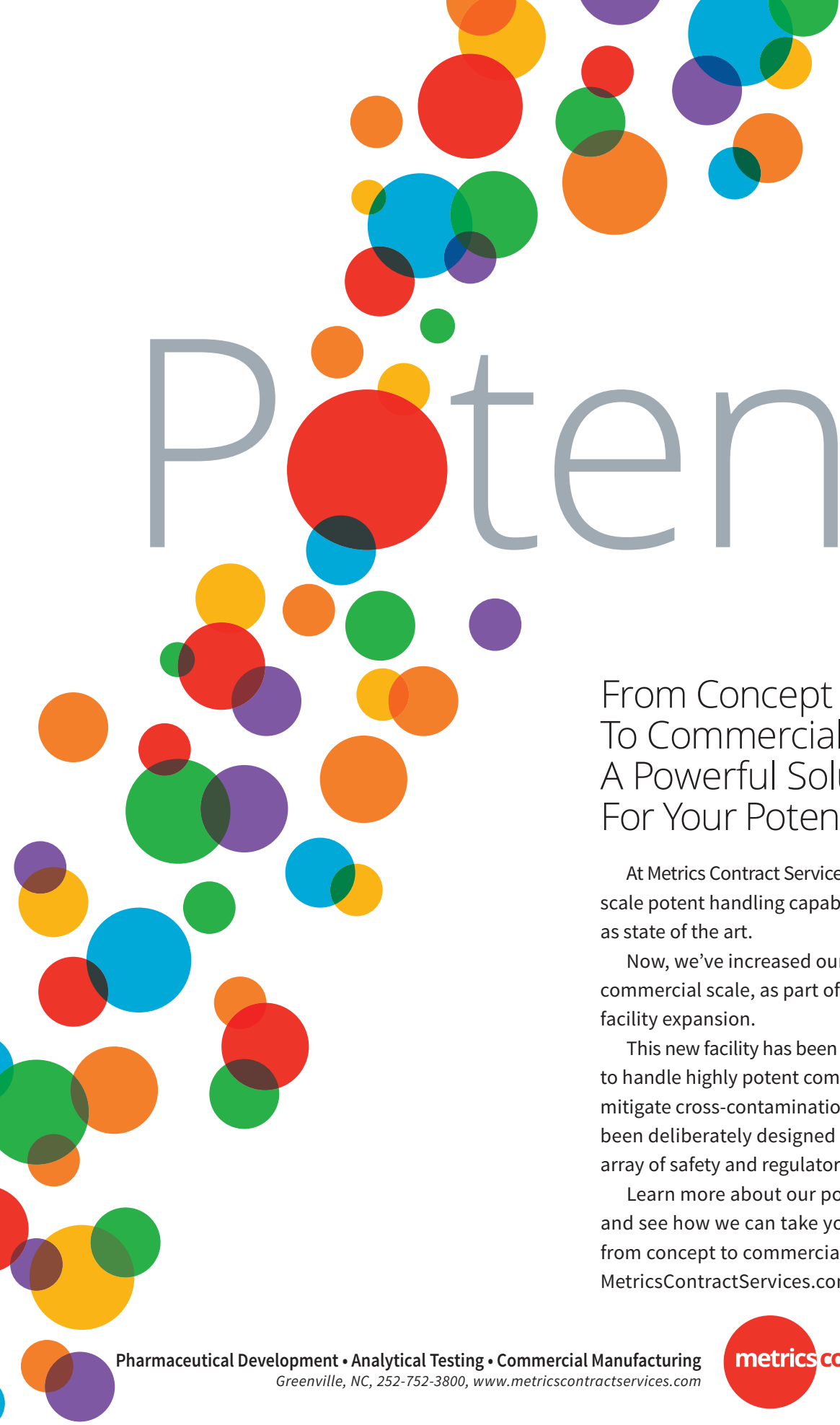
An API can be used with a medical device to enhance the performance or safety of the device, or both. A good example of this would be a collar added to a pacemaker lead that is made from a mixture of silicone and Dexamethasone. The Dexamethasone enhances the function of the pacemaker lead by reducing the inflammation and swelling post-implantation at the surgical site.

On the other hand, medical devices can be used as a delivery method for an API. Inhalers and insulin pumps are good examples of devices that focus on drug delivery, with the drug and the device acting independently.

Implanted contraceptives combine a drug reservoir with a rate-release control membrane to elude a hormone in a closely controlled range over a lengthy period of time. In this case, the device function and the drug are functionally intertwined, with the drug and device attributes being combined to provide the specified therapeutic dose. An API may be combined with polymers in many ways; two of the most common are mixing an API with a polymer, such as silicone, prior to manufacturing the component or drug formulation, or adding the drug to the component after component fabrication. Each of these approaches have advantages and limitations.

Mixing the API with a polymer

In most controlled-release drug delivery applications, the API is added to the base polymer before the polymer is



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formed into its final shape. When the materials to be mixed are combined in a closely controlled process, the end result is that the final dosage is controlled well within dosage specifications. In many manufacturing operations, material handling and mixing are completed in single-use, disposable vessels so that safety and contamination controls can be more easily implemented. Single-use systems are one way that the burden of validated cleaning methods is reduced, especially during early preclinical and clinical development.

At commercial scale, dedicated equipment and manufacturing cells are frequently used so that cross-product and cross-facility contamination risks are more readily controlled. At all stages, containment and cleaning plans must be designed and implemented as part of a risk-based hazard assessment.

Developing infused silicone devices

There may be several advantages to adding an API to a previously manufactured product. Some of these advantages are: the manufacturing process for the initial product may continue without modification, the handling of the API/solvent mixture is performed in an isolated environment separate from the remainder of the facility, and the product lead time is relatively short compared to a product where the API is mixed with the polymer prior to shaping. There are several predicate products to be found, so development paths can be shortened.

The first step in developing a silicone implant to which the API may be added is by working with a silicone component manufacturer with an understanding of the silicone and the API chemistry in general, and the drug solubility in particular. Understanding the drug solubility is critical to determine which solvent is best for the application. The API must be dissolved in a solvent that can permeate the silicone. The device is immersed in the solvent/API solution, and in this way, the solvent can penetrate the silicone material molecular chains, with the drug molecules left behind after the solvent flashes off. Chloroform is a commonly used solvent; toluene and acetone are also options.

The length of immersion is determined by a number of factors, including the type of drug, the overall device design, the thickness of the silicone wall, the density of silicone being used, and the size of the part. Typically, a short series of controlled tests (two to four) are completed to determine the optimal immersion time and establish a range of immersion times and concentrations of the drug/solvent combination.

There are limitations to this process; the content control and uniformity of the API in the component will be less than when adding an API to the base polymer; the drug content as a mass ratio is generally lower; and the total time of drug release is limited to shorter times (e.g., days or weeks).

Bio-absorbable devices for drug delivery

Polyvinyl acetate (PVA) and ethyl vinyl acetate (EVA) are bio-absorbable polymers that can be used to help control the rate of release of a variety of drugs. Small-scale implants that are completely absorbed once the drug has been fully released have the potential to reduce post-surgical infections and increase medication compliance.

Similar technology is under development for ophthalmic applications. Rather than prescribing eye drops, which have a low rate of patient compliance and are prone to dilution from tears, a drug delivery on-lay containing medication may be placed under the eyelid by a physician. It would deliver a minute amount of medication (measured in micrograms per day), and the polymer wafer is absorbed at the same rate as the drug.

These devices can be used for delivering minute amounts of a drug over a period of days or weeks. Typical drug delivery rates range from 10–20 micrograms per day, and the drug reservoir may hold 2–100 milligrams in total.

Key considerations for product development

When designing any device combining a polymer with an API, one of the first considerations is whether the device will stay in the body or be absorbed. Silicones, for example, are meant for long-term use, while PVAs or EVAs are bio-absorbable.

Other considerations include:

- The dosage to be dispensed
- Whether the dosage is flat or varied (i.e., a bolus of drug immediately after device implantation followed by a tapering dose)
- The frequency of the dose that will be dispensed
- The overall length of time the drug will be dispensed.

It's important to work with a vendor experienced with combination devices to determine the viability of a proposed new device. Look for a vendor prepared to take a project from early-stage feasibility through development, clinical trials, and commercialization. The contract development and manufacturing organization selected to be a development partner must have the quality systems required for cGMP manufacturing, which starts with a commitment from upper management to high-level quality systems and safety standards.

Looking forward

As with any new technology, the vast proportion of formulation work comes at the initial stages of developing a combination product. Pharmaceutical scientists must develop hypotheses and work with development and manufacturing partners to align with therapeutic, quality, and commercialization goals. Additionally, devices with multiple APIs may begin appearing on the market, leading the way to personalized drug therapy in the future.

As these devices are tested, improved upon, brought into clinical trials, and commercialized, the methodologies for creating them should be established early in the development program. It is crucial to characterize the manufacturing processes as early as possible to achieve quality and economic value for new medical and drug products. **PT**

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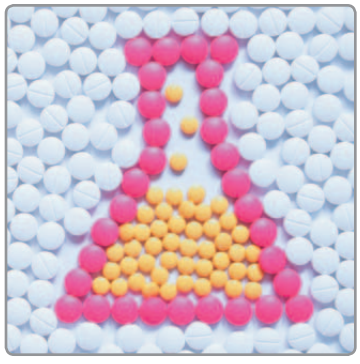
Classifying Potent and Highly Potent Molecules

Jeff Pavlovich



ORAWAN PATTARAWIMONCHAI/ SHUTTERSTOCK.COM

Determining how much containment is needed for API handling requires evaluation of multiple factors. The author examines exposure limits, handling challenges, and assessment strategies.

Highly potent drugs represent a growing proportion of medicines, including therapies in development and those commercially available. As older products reach patent expiry, generic-drug companies are also moving into this space, creating an increasing demand for capability and capacity to manufacture highly potent APIs (HPAPIs), particularly for contract manufacturing organizations (CMOs).

A significant proportion of HPAPIs are in the oncology field, and as approximately one-third of all new drug approvals are currently cancer medicines, this represents a substantial market opportunity. Other therapeutic areas where drugs may be highly potent include asthma and pain management.

The chemistry to make these molecules is not necessarily difficult; however, the greater challenge is in the handling and containment of them to ensure operator and environmental safety. It is vital that a careful assessment is made of the hazards posed by each individual product, reagent, and intermediate involved in the synthesis ahead of manufacture. If the risks are underestimated, people within and around the plant will be in danger. Conversely, if the risks are overestimated, the result will be excessive amounts of money spent on containment and an increase in project costs.

A compound is deemed to be potent in pharmaceutical terms if it has an eight-hour, time-weighted average occupational exposure limit (OEL) of 10 μg/m^3 or less. There is, however, no formally agreed definition of the OEL level that constitutes a "highly potent" compound. To add to the confusion, the same compound might be classified differently by individual risk assessors. This variability in classification is exemplified by a study carried out by Cambrex in which a panel of 38 molecules was sent to three risk assessors. Three different results were provided: one assessor deemed five of the 38 to be highly potent, one assessed 37 of the 38 to be highly potent, and the third fell somewhere between the two extremes.

The subjective nature of these results highlights that any CMO managing a facility to manufacture multiple APIs that may, or may not, be highly potent should consider each project on a case-by-case basis. A flexible approach allows manufacturing techniques, equipment, and containment options to be tailored to the molecule's properties, and the

Jeff Pavlovich is senior process safety engineer at Cambrex.

requirements of each individual step of the synthesis. The result should be increased safety, lower costs, and enhanced capacity for the manufacturing of HPAPIs.

Risk determination

When determining risk, the starting point is the OEL and other safety-related properties of the molecule determined as part of the drug development process. Once an investigational drug reaches the large-scale manufacturing stage, extensive safety data will have been compiled, including results from preclinical toxicology assessments, animal studies, and early-stage clinical trials.

These data on potential hazards and dose–response effects are used as a basis by experts in risk assessment to generate OELs and occupational exposure bands (OEBs) that allow informed decisions to be made about engineering strategies and industrial hygiene requirements. Appropriate containment and personal protective equipment should be supplemented by comprehensive training to ensure their proper use.

There is an important caveat. Although toxicological data offer a useful starting point, there is a difference between potency and toxicity. Potency is a measure of how much of the API is required to have a therapeutic effect; toxicity is a measure of its adverse effects. A cytotoxic drug to treat cancer may be extremely toxic but its potency might be low, and therefore, side-effects are likely. Conversely, for some drugs

Figure 1: Points of departure. NOEL is no observed effect level; NOAEL is no adverse event level; LOEL is low effect level; LOAEL is low adverse effect level; MTD is maximum tolerated dose; BMDL is benchmark dose level; LD50 is median lethal dose; ED50 is median effective dose; and TD50 is median toxic dose.

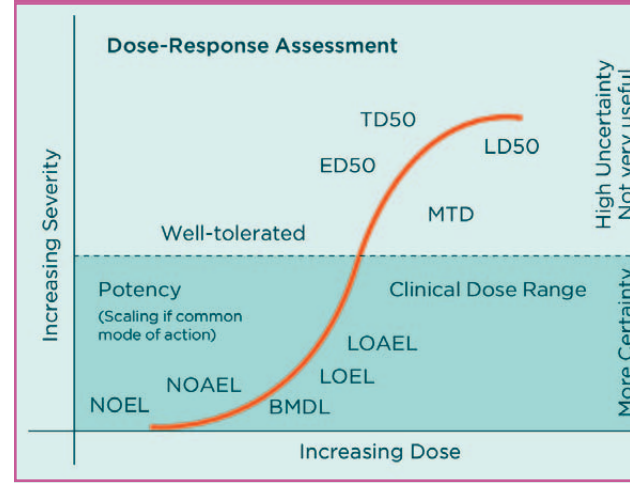


FIGURE COURTESY OF THE AUTHOR

Table I: Contributors to uncertainty.

Area of uncertainty	Uncertainty factors
Intraspecies variation	10
Interspecies variability	2–12
Study duration	3–10
Low-effect level (LOEL) to low-adverse-effect level (LOAEL)	10
Database sufficiency	1–10
Severity of effect	1–10
Bioavailability	1–10
Bioaccumulation	1–10
Pharmacokinetics	3–10
Route-to-route	3–10

Modifying factors
Slope of dose-response curve
Choice of critical effect
Susceptible subpopulations
Clinical significance of critical effect
Reversibility of critical effect
Relevance of critical effect on workers
Read-across similarity
Lack of independence for uncertainty factors

that only require very small doses to have a medical benefit, the dose that causes side-effects may be substantially larger. The handling requirements in the manufacturing plant will be very different for the two.

Toxicology data gleaned from preclinical research or clinical trials are not designed for direct application to OELs, either. The aim of an early-phase clinical study is to determine optimal doses, balancing therapeutic benefit and what patients can tolerate. There is a huge difference between exposure in this context, and the inadvertent inhalation of dust in a manufacturing facility; there is no direct correlation between these clinical trial data and the safe exposure level for operators.

The data will, however, provide indications to issues that might occur with acute exposure. If they highlight issues such as respiratory problems, lachrymatory issues, adrenergic concerns, or somnolence, for example, acute problems might be anticipated in manufacture. There may be indicators toward chronic exposure issues, also, if there are indications that the compound might be carcinogenic, mutagenic, a sensitizer, or a clastogen.

With this information in hand, the next step is to identify any critical effects that exposure might have, such as target organ toxicity or pharmacological effect, and the dose-response curve. However, inter-person variation makes it difficult to make a definitive risk assessment.

At the lower end of the dose–response curve (**Figure 1**) is no-observed-effect level (NOEL), where the chemical causes no effect at all. The next point moving up the curve is the no-adverse-event level (NOAEL), which is commonly cited in risk assessments. Next, there are the analogous low-effect level (LOEL) and low-adverse-effect level (LOAEL), and then doses that are well tolerated, followed by the maximum tolerated dose (MTD). Past this point, the APIs are likely to be hazardous. In animal tests, at the ED50 point, half of the animals will experience an effect; at the TD50 point, half will experience toxicity; and at the LD50 point, half the study animals will die at that level of exposure.

The OEL equation (**Equation 1**) includes uncertainty factors (**Table I**) that compensate for unknowns. The numerator comprises factors that will increase occupational exposure, while the denominator includes those that will reduce it, including uncertainty factors. Those components that can contribute to uncertainty include variation between species and between subjects, the duration of the study, the severity of the effect, bioavailability and bioaccumulation, and pharmacokinetics.

$$\text{OEL } (\mu g/m^3) = \frac{\text{PoD x BW}}{\text{UFc X MF x V}} \qquad \text{[Eq. 1]}$$

Where:
OEL is occupational exposure limit
PoD is point of departure for extrapolation (mg/kg-bw/day)
BW is body weight (kg)
UFc is composite uncertainty factor
MF is modifying factor
V is volume of air breathed during work shift (m^3)

Modifying factors are also considered by some risk assessors, including the slope of the dose–response curve, and the choice of critical effect and its clinical significance, its reversibility, and its relevance to workers. Susceptible subpopulations and read-across similarity may also be considered, as may a lack of independence for uncertainty factors.

This uncertainty is at the root of the variability in risk assessments. Depending on the magnitude of uncertainty values that are applied, and whether modifying factors are given weight, there is the potential for as much as eight orders of magnitude of difference in the OEL determined by individual assessors. Reconciling this variability in the final risk assessment is a major challenge.

The solution lies, at least in part, in applying real-world context to the uncertainty factors. Perhaps the most important is the acceptable exposure risk for an individual operator, and even for the most conservative risk assessor, a one-in-one-thousand risk may well be more realistic than the one-in-one-million risk to be an appropriate likelihood of an exposure happening. The one-in-one-thousand risk is not without context: it is commonly cited as the chance of a severe injury in a hazardous work environment.

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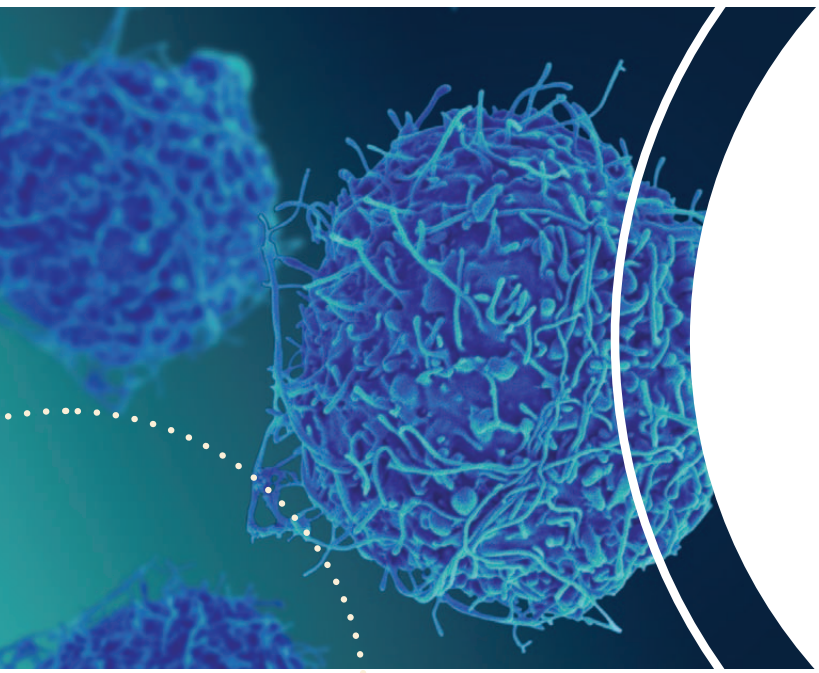

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Lifecycle-Based Process Validation Emphasizes the Need for Continued Process Verification

Ajay Pazhayattil, Naheed Sayeed-Desta, and Marzena Ingram

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A year's worth of FDA warning letters suggest that API and finished drug manufacturers should strengthen their approach to continued process verification.

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In 2011, when FDA revised its process validation guidance (1), it introduced the idea that validation must continue throughout the lifetime of a pharmaceutical product. FDA advocated three stages:

- Process design, using the principles of pharmaceutical quality by design (QbD)
- Process performance qualification (PPQ)
- Continued process verification (CPV).

Pharmaceutical manufacturers have been developing novel methods and solutions to support this new definition of process validation, and FDA has been encouraging science- and risk-based approaches for all three stages.

Other regulatory agencies have also embraced the lifecycle approach to process validation, including the International Council for Harmonization (ICH) in its *Q8, Q9, and Q10 Questions and Answers (R4)* (2) guidance for industry. ICH views the entire product lifecycle as: development, technology transfer, manufacturing, and discontinuation (3).

Best practices call for approaches such as:

- Taking a design-of-experiments (DoE) approach to product development, sampling, and testing plans
- Determining the number of PPQ batches
- Using data-driven statistical tools for CPV.

The European Medicines Agency's (EMA) 2014 process validation guidance, the World Health Organization's 2015 Appendix 7, and the Pharmaceutical Inspection Cooperation Scheme (PIC/S) 2015 Annex 15 all reflect the expectation that process validation should continue throughout the lifecycle of the process. Pharmaceutical manufacturers would do well to take an integrated lifecycle approach to process validation that works across multiple markets.

As the industry's approach to lifecycle-based process validation has evolved, some companies now divide Stages 1, 2, and 3 into the following:

- Stage 1A – Product Development, Stage 1B- Scale Up
- Stage 2A – Equipment/System/Utility/Facility Qualification, Stage 2B – Process Performance Qualification

- Stage 3A–a heightened verification program for newly introduced molecules and Stage 3B-routine continued process verification. Implementing the process validation lifecycle approach globally demands that pharmaceutical manufacturers be especially careful in selecting the most effective statistical tools and Stage 3 strategies (4).

A good knowledge-management strategy is essential, starting from Stage 1 to Stage 3 of the process validation lifecycle. Scientifically identifying sources of variability requires a robust QbD-based product development program along with a Stage 3 CPV program that allows for continual gathering of product and process knowledge.

Learning from process drift

Process drifts, or times when the process fails to perform at its best, trigger identification of sources of variability, ensuring improved control and allowing for continuous improvement. Ongoing collection of product and process knowledge is required for continuous improvement, and also to improve the development process for similar products (5).

This article asks how well pharmaceutical manufacturers have been addressing new process validation requirements by analyzing FDA warning letters (WLs) from 2017 to date. The goal of this study is to understand which parts of the process may need to be strengthened in order to improve regulatory compliance and minimize risk.

Since the FDA process validation guidance is applicable to drug substances, drug products, and biologics, insights from WL assessments (6) can provide ample supporting evidence to justify an integrated approach to process validation.

For this research, 85 FDA WLs issued in 2017 and 2018 were analyzed, 61 for 2017 and 24 for 2018. Inadequacies were found in both API and finished pharmaceutical facilities, but occurred mainly in finished pharmaceutical facilities, as outlined in **Table I**.

In 2017 and 2018 FDA warning letters, process validation issues were more frequently noted in finished pharmaceutical than in API manufacturing sites, with noncompliance increasing by 5% between 2017 and 2018. Of the warning letters analyzed, 40% contained observations that were related to process validation. Since 2017, 29 finished formulations sites have been found to be noncompliant with process validation approaches, and the number of facilities that were out of compliance increased in 2018 (**Figure 1**).

API facility issues

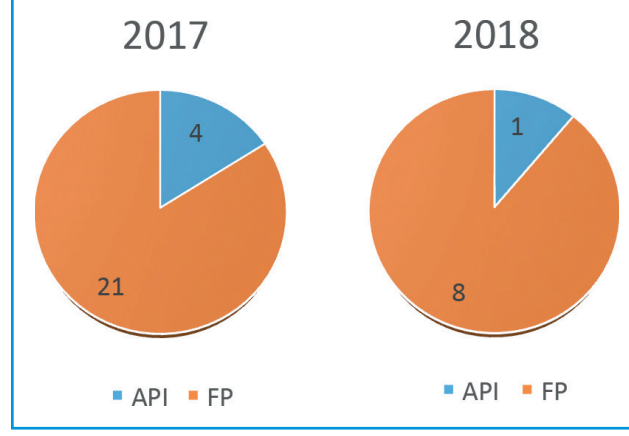
Approximately 20% of the API sites that received warning letters during the period under examination had problems that were related to PV noncompliance. Two of the five warning letters related to API sites cited inadequate process control monitoring, resulting in the inability to ensure stable manufacturing operations and consistent drug quality.

Regulators who had inspected the facilities identified the strong need for engaging a qualified consultant to assist the organization in meeting current good manufacturing practice (cGMP) requirements. Another warning letter cited inadequacies in the sampling plan during the PPQ stage. It highlighted the need for a statistically sound sampling and testing plan as stipulated in the PV guidance.

Table I: An overview of process validation (PV) observations.

Year	% WL with PV Observations	% API Sites with PV Observation	% Finished Pharma Sites with PV Observations
2017	41%	24%	48%
2018	38%	13%	50%
Avg.%	40%	19%	49%

Figure 1: Finished pharmaceuticals and API sites with process validation observations. FP is finished pharmaceutical.



In addition, inspectors found that the manufacturer was not monitoring critical process parameters adequately. In a third API process-related observation, the regulator cited that the organization did not demonstrate adequate process understanding, which includes failing to consider operating parameters for critical operations. Regulators focus on all three PV stages during an inspection. In its inspection, FDA staff called for hiring external help, especially when the manufacturer could not implement the Stage 3 CPV program independently.

Finished pharmaceuticals facilities

In 14 warning letters, regulators noted the manufacturers should follow FDA process validation guidance for the process validation elements. Additional assessment revealed a consistent pattern. As the warning letters make clear, the following are very important in process validation:

- Having a data-driven and scientifically sound process-validation program that appropriately identifies sources of variability
- Performing process performance qualification studies
- Establishing an ongoing program for monitoring process controls to ensure stable manufacturing operations and consistent quality.

FIGURES COURTESY OF THE AUTHORS.

The problem that inspectors most often found at finished pharmaceutical facilities was failure to establish a continued process verification program to identify sources of variability. This gap was cited in 17 warning letters. Eight of the citations pointed out that the manufacturer did not perform PPQ studies.

Regulators ... are encouraging the use of data-driven, science based approaches to process validation ... which will require that [pharmaceutical manufacturers] invest ... in establishing a Stage 3 CPV program and team.

Observations about Stage 3 CPV-related operations were found across prescription, over-the-counter (OTC), and sterile manufacturing sites alike. The regulator used consistent language and quoted from the *21 US Code of Federal Regulations (CFR)* Part 211, Subpart F- Production and Process Controls, Sec. 100–Written procedures, deviation (a). The *21 CFR 211.100 (a)* section states: "There shall be written procedures for production and process controls designed to assure that the drug products have the identity, strength quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit"(7).

There were five instances in which regulatory inspectors noted a failure to prevent microbial contamination in sterile manufacturing, including lack of established procedures as well as inadequate validation of aseptic manufacturing processes and sterilization. The drug manufacturer is required to implement elements of cGMPs for sterile drug products using aseptic processing. Additional observations that were cited included deficiency in performing smoke studies for classified areas, which include Restricted Access Barrier Systems (RABS).

Conclusion

For this assessment, warning letter trends were analyzed to provide manufacturers with some insight into regulators' objectives. Both API and finished pharmaceutical manufacturing sites are consistently being cited for violating best practices in recent process validation guidance. Analysis of the observations confirms the need for a well-defined continued process verification program that continually monitors the sources of variability and enables an organization to embark on continuous improvement initiatives prior to encountering quality issues.

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Regulators around the world are encouraging the use of data-driven, science-based approaches to process validation. In some cases, inspectors have suggested that manufacturers enlist the help of qualified consultants, which will require that they invest time and resources in establishing a Stage 3 CPV program and supporting team.

More biopharmaceutical manufacturers are now striving for data-driven approaches to Stage 3 process validation, and solution providers are offering integrated software to help manage such programs. The convergence of regulatory guidance, current inspection trends, and the emergence of solutions allows existing monitoring programs to be enhanced, but there will likely be a need for additional elaboration and training across quality, operations, R&D, and regulatory functions.

Ensuring that process validation programs and training bridge different functional groups within the organization helps all groups understand their role in enabling continuous improvement. This kind of approach will help manufacturers prevent process failures, and can also help guard against having people overreact to individual events. It can also ensure that they catch sources of variability that might otherwise go undetected.

Authors' note: This article was prepared by the authors in their personal capacity. The opinions expressed are their own and do not reflect the view of their employer, government, or any agency with which they are affiliated.

References

1. FDA, *Guidance for Industry: Process Validation-General Principles and Practices*, (Silver Spring, MD, Jan 2011).
2. ICH, *Q10 Harmonized Tripartite Guideline, Guidance for Industry: Q8, Q9 and Q10 Questions & Answers (R4)* (ICH, November 2010), ich.org, www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/Q-IWG_QAs_Step4/Q8_Q9_Q10_Question_and_Answer_R4_step_4_November_2010.pdf
3. ICH, *Q10 Harmonized Tripartite Guideline, Pharmaceutical Quality Systems*, (ICH, June 2008), *ich.org*, www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf
4. ISPE, *Pharmaceutical Engineering*, September 2017.
5. Parenteral Drug Association (PDA), "How Global Pharma Organizations Can Achieve Process Validation Success," *PDA Letter*, February 2017.
6. FDA, Warning Letters and Notice of Violation Letters to Pharmaceutical Compliance, Silver Spring, MD, May 2018, *fda.gov*, www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/default.htm
7. FDA, *Title 21, Food and Drugs, 21 Code of Federal Regulations 211.100(a)*, *accessdata.fda.gov*, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.100 **PT**

Reducing Cleanroom Complexities and Cost

Sidney Backstrom and Maik Jornitz

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Why shouldn't biopharmaceutical manufacturers be able to leverage standardized construction practices to improve time to market?

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For pharmaceutical and biopharmaceutical manufacturers today, a key success factor is time to market (1–4). When it comes to processes and manufacturing facilities, time to the first product run is crucial. The faster a drug moves through the development pipeline and the faster a facility is up and running, the higher the return on investment. In addition, a fast-moving facilities project can allow capital expenditures to be delayed until later in the development cycle, minimizing risks and maximizing the amount of cash on hand until needed.

The traditional approach

Traditional facility designs and infrastructures do not permit such fast-track implementation (5). It takes months to generate designs and even longer to build these manufacturing sites, and construction proceeds sequentially.

The process generally follows this pattern: a building shell is built first, followed by utilities, then ancillary and cleanroom spaces, and finally production equipment is installed. Typically, this approach means a time-to-first-product run of 24–48 months, depending on the size of the facility. The same is true for smaller projects such as laboratories.

Modular options

Modular construction onsite involves building processing space at the ultimate production location using modular wall panels. Many companies provide such panels. This approach differs from traditional construction in that the panels are rigid and therefore do not require framing material. The panels also come in a variety of sizes, reducing the amount of cutting required onsite.

The panels also reduce the amount of finishing work that is required, because they are supplied as finished pieces such as coving at the wall-to-ceiling and wall-to-floor connection points. The use of standardized components can shorten the design phase for modular panel projects, compared with the time required by traditional approaches. Significant engineering knowhow is still required, however, to make modular construction work.

Because this approach reduces the amount of onsite construction required, these projects can be completed faster than a traditional construction approach, with project time-

lines that can range from 18 to 36 months depending on the size of the project.

Prefabricated cleanrooms

Prefabricated cleanrooms are modules that are built offsite that provide clean space including floors, walls, ceilings, windows, and doors in appropriate finishes. In some instances, such modules include their own mechanical space where automation equipment such as programmable logic controllers (PLCs), heating, vacuum and air conditioning (HVAC) equipment, fire suppression systems, utility connections, etc. are housed.

The cleanrooms are built entirely at a vendor's manufacturing site. At the close of the manufacturing process, they are factory tested. After this testing, they are shipped and moved into the ultimate host facility. Due to the utility infrastructure within the cleanrooms, connections to the host facility are minimal, and infrastructure within the host facility is also minimal. High level advantages include being able to build the modules rapidly without the need for special permits, the lack of required infrastructure at the ultimate destination, the ability to move and repurpose the cleanrooms, and depreciating the cleanrooms on an accelerated basis as process equipment, as opposed to the traditional facility timeframe (6).

Engineering expertise is required both for the cleanroom and the outer structure. Compared with the fairly standard cleanroom approach in most cases, however, there is less to engineer using this approach.

Figure 1: Timelines for different types of plant construction projects.

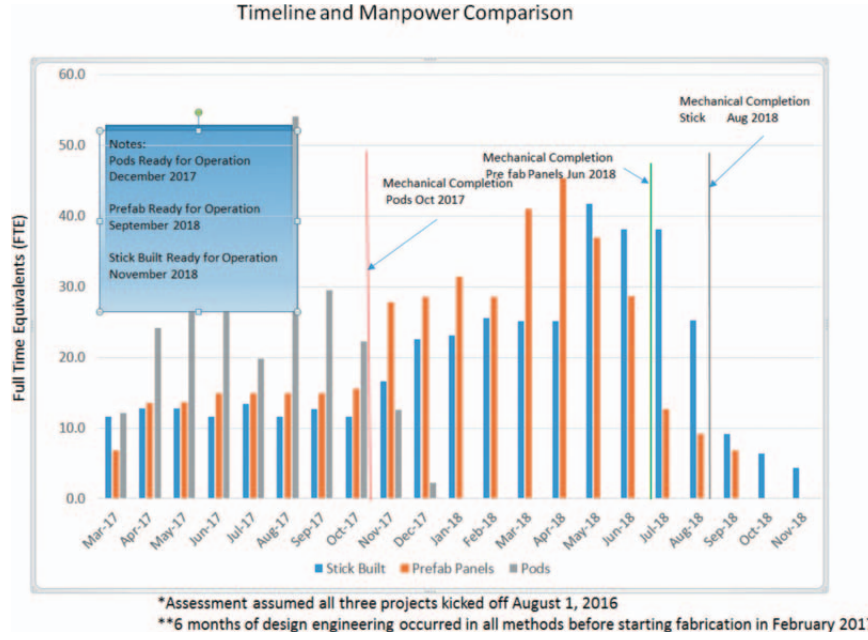
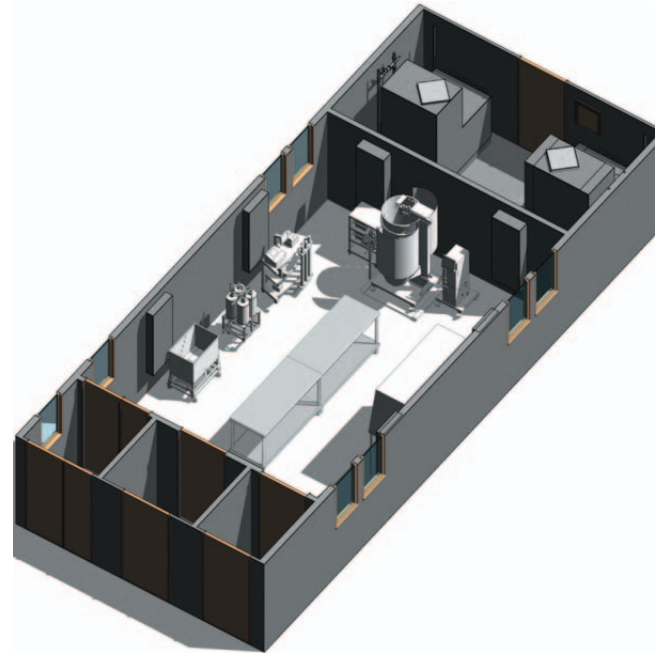


Figure 2: A prefabricated cleanroom POD, containing controls and utilities.



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A leading architecture and engineering firm considered the amount of time required to build a 2000L monoclonal antibody (mAb) facility. The study considered three types of facility options: traditional, modular wall panel, and prefabricated cleanrooms. **Figure 1** presents findings.

As can be seen in **Figure 1**, the time differences among the three models are substantial, with prefabricated systems being much faster. For one manufacturer, using the prefabricated approach allowed the facility to be ready for operation 16 months after the start date (1) compared with 25 months

for the paneled approach and 27 months for the stick-built approach. Construction of the prefabricated system solution was faster due, in part, to the fact that the cleanrooms were built in parallel with the building or refurbishment of the host facility (**Figure 2**). Such an approach is not possible with the other construction options, because the structures must be constructed after the host facility is substantially complete.

An additional factor that also saves time, which this study did not consider, is the fact that prefabricated cleanrooms use standard designs. Instead of creating new designs from scratch, these standard designs can be used to reduce the design time and cost effort.

Could standardization lead to other advances as it has in other industries, enhancing speed to market without sacrificing quality or utility?

As noted, some standardization of cleanroom options can reduce the time required to build out a facility, using a prefabricated approach. But could standardization also lead to other advances as it has in other industries, enhancing speed to market without sacrificing quality or utility?

Procter and Gamble showcased an example of what might be possible for pharma at the International Society for Pharmaceutical Engineers' (ISPE's) 2014 Annual Meeting. The presentation discussed the use of standardized shell buildings that could be erected in weeks. Parallel to the construction of the building shell, prefabricated manufacturing modules were assembled and then added into the shell when it had been completed.

Mixing and matching, in synch with demand

The prefabricated manufacturing modules were standardized and could be mixed and matched into the shell building. Depending on demand, they could also be exchanged, in case regional demand for one product rose or fell. Standardizing the system created budget and timeline robustness, as well as scaling effects to reduce costs (7).

Another example comes from the automotive industry. In automobile manufacturing today, the core product is standardized, but also configurable, with options that are related to aesthetics or performance. Standardizing the core product keeps costs low and delivery times short, and adding options to that core does not increase either factor significantly.

If carmakers sought to design each vehicle anew, with no standard platform in place, costs would be astronomical and the efficiency of production and delivery would be exceedingly low. The question is: Can the biopharmaceutical industry mirror these two examples, especially in the cell and gene therapy space? Why shouldn't it be possible to standardize these processes, unit operations, and surrounding cleanroom infrastructures all the way to the facility platform?

Standardization vs. *status quo*

Why has such standardization been achieved, or even become the norm, in other industries but not the biotech industry? Is it because the engineering or processing needs are that much more sophisticated than other industries, or is it because the supplier infrastructure in the biotech industry prefers self-preservation to innovation?

More to the point, couldn't a prefabricated, standardized but configurable cleanroom infrastructure solution be provided much like a car, bioreactor, or filler? Shouldn't such infrastructures be available from a catalogue where they can be chosen for delivery? And is there any reason why that cleanroom couldn't be delivered in 48 hours?

Amazon and FedEx deliver hundreds of thousands of items in two days. Mobile homes can be ordered. Contractors build and sell "spec" houses every day. So why can't biotech companies choose from available options instead of re-inventing the wheel every time they have to build a new manufacturing facility?

The goal for the industry should be to configure a cleanroom on-line or at a showroom and get it delivered consistently with the same quality at a fixed price and timeline. End-users who adopt this standardization approach will gain desired speed, with tremendous flexibility and greatly reduced costs. That can only be good for the industry and, ultimately, for the patients it serves.

References

1. H.L. Levine, et al., "Efficient, Flexible Facilities for the 21st Century," *BioprocessInternational.com*, 2012, www.bioprocessintl.com/manufacturing/facility-design-engineering/efficient-flexible-facilities-for-the-21st-century-337813/.
2. J. Markarian, "Continuous Solid-Dosage Manufacturing Platform Nears Prototype Installation,"*Pharmtech.com,* November 2, 2014, www.pharmtech.com/continuous-solid-dosage-manufacturing-platform-nears-prototype-installation.
3. P. Thomas, *pharmamanufacturing.com*, January 10, 2012, www.pharmamanufacturing.com/articles/2012/008/.
4. A. Pralong"*Biopharma Asia Magazine*, 2 (1), pp.12-14 (2013).
5. P. Almhem, "Modular/Flexible Facilities," *Pharmaceutical Processing*, July/August, pp. 28-30 (2014), www.digital.pharmpro.com/pharmaceuticalproducts/july_august_2014?pg=28#pg28
6. M.W. Jornitz, "Podified Manufacturing Facilities and Risk Mitigation of Aging Pharmaceutical Facilities," April 2014, *pharmaceuticalonline.com,* www.pharmaceuticalonline.com/doc/podified-manufacturing-facilities-and-risk-mitigation-of-aging-pharmaceutical-facilities-0001 pro.com
7. Press Release, *pharmaceuticalonline.com,* September 27, 2013, www.pharmaceuticalonline.com/doc/gea-g-con-announce-collaboration-with-pfizer-requirements-of-pharmaceutical-development-and-manufacturing-0001 **PT**

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How to Address Roadblocks During Technology Transfer: A CDMO's Perspective

Baerbel Hinneburg

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Real-life examples illustrate how to reduce the risks for each transferring partner and ensure that the development process meets regulatory requirements.

Baerbel Hinneburg, PhD, is Director Technology & Process Transfer at Vetter.

Technology transfer can be a daunting and high-risk task. A technology transfer of a commercial aseptic manufacturing process is much like the introduction of a product to a new manufacturing facility. The process of achieving an exchange of information that leads to a successful execution and quality manufacturing of a drug product involves numerous steps and challenges. The stakes are high, and the processes involved are complex. Strict regulatory requirements and attention to detail are required to achieve success. The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve project realization. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach, and ongoing continual improvement.

The necessities of a successful technology transfer

As with any complex and intricate action, planning and execution for a technology transfer is critical. It begins with the creation of a team that has the necessary skill sets and amount of know-how in addressing multiple areas of the process. A dedicated technology transfer team includes experts from development, production, quality assurance, regulatory affairs, quality control, and qualification/validation, among others. Together, they are responsible for facilitating and executing the process and coordination with the technology transfer/project leader. Roles and responsibilities for all team members of the facility involved must be agreed upon, and a system that enables adequate communication and feedback of information, including a confidentiality agreement between parties, established.

From a regulatory perspective, a technology transfer of an aseptic commercial product from one cleanroom to another may not much differ in time and effort compared to initial development and design of the manufacturing process. Thus, the scope of such a transfer is determined by multivariable aspects, including:

- Filing strategies
- Special arrangements with authorities

Table I: Example of tech transfer. An initial paper-based assessment (gap analysis) is the basis and provides indications for necessary budget, timing, and resources (data from Vetter). CQA is critical quality attribute.

Parameter/ Equipment	Cleanroom A	Cleanroom B	Change Yes/No	Documented in filing dossier	Impact on quality attributes	Potential risk
Mode of dosing	Rotary piston pumps from supplier A, diameter 8 mm	Rotary piston pumps from supplier A, diameter 12 mm	Yes	Yes	Fill volume	Medium, calibration curve of both piston covers the required fill volume, wide specification limits (+/- 5%), process capability needs to be verified on the filling line
Number of fill heads (pumps)	2	8	Yes	No	No	Low, dispensing mode and velocity are equal, process capability needs to be verified to demonstrate that all pumps run on target
Nitrogen flush	Nitrogen flush installed	Nitrogen flush installed	No	No	CQA (Oxygen level in the syringe head space)	High, <10% on stability, efficacy of nitrogen flush is not known, studies required

- The commitment in accepting potential operational and methodical changes enabling the achievement of state of the art.

Commercial transfers can take more than one year; not only because of a regulatory change and the potential risk of facing unforeseen new challenges, but also because it takes time for regulatory bodies to accept the approach and be convinced that there are no impacts to the specified quality attributes.

Drivers for a technology transfer

For many pharma and biotech companies, a back-up strategy is necessary for risk management to provide an adequate supply for the patient. The firm may also lack the appropriate resources/capacity for process optimization, commercial production, secondary packaging, supply chain management, and scale-up from clinical production to larger commercial production. The best approach to enable a successful outcome is usually through working with a contract development and manufacturing organization (CDMO) that has considerable experience in technology transfer. A skilled CDMO can also help create a lifecycle management plan in the event of a change of packaging to support patient convenience or improvement of the manufacturing process.

Challenges for the CDMO

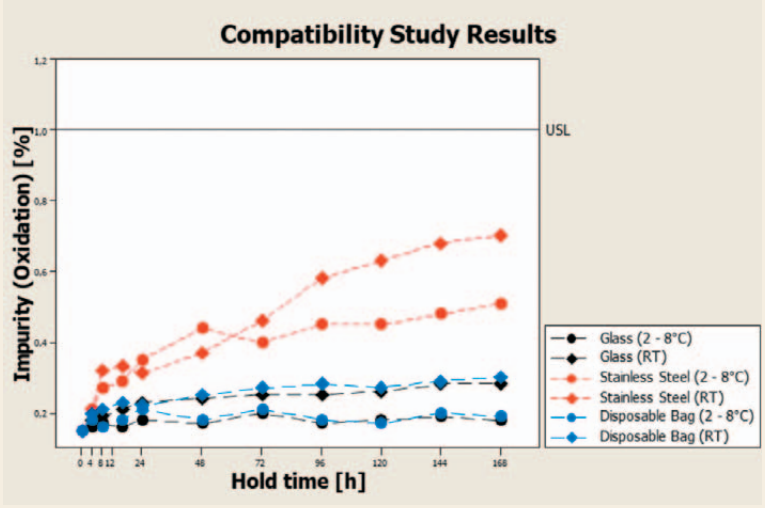
Technology transfer is one of the most complex and time-consuming processes for a CDMO, especially because multiple partners and sites are involved. On one hand, there is the sending unit, defined as the involved disciplines within the organization where a designated product, process, or method is expected to be transferred from; and on the other hand, there is the receiving unit, which are the involved disciplines at an organization where a designated product, process, or method is expected to be transferred and executed.

A successful transfer of a manufacturing process is based on appropriate relevant documentation and on the application of risk management elements according to the International Council for Harmonization (ICH) Q8 guideline (1). The existing knowledge gained from the development of the drug product and the experiences of the manufacturing process have already identified the critical quality attributes (CQAs) that must be controlled and tested to achieve the target product profile (see **Table I**). Therefore, the following activities are major elements of a tech transfer to achieve a robust, reproducible manufacturing process at the receiving site:

- **Combination of gap and risk analysis** to assist in identifying and evaluating any differences between transfer sites that have potential impact on CQAs, to identify any process steps that become critical process parameters (CPPs) that may have not been obvious on the first level of information.
- **Process design** at the receiving site to accommodate the known and new identified CPPs that must be controlled to meet CQAs.
- **Process qualification** to verify that the process enables constant quality and to establish a control strategy at the receiving site. Identifying and controlling sources of variability in material and processes is also crucial to successful technology transfers.

Additionally, knowledge of filing strategies is essential, because some countries have specific requirements for commercialization that can influence the scope of process qualification strategies, such as bracketing strategies, batch sizes, or holding times. Regulatory constraints can also influence the change of a production environment. Further, the exchange of processes including equipment and facilities, cleaning and sterilizing procedures, input parameters, and in-process controls all within, or between, production sites must be assessed, and documentation of the transfer with all its contracts, protocols, reports, and

Figure 1: A compatibility study showed the differences in impurity levels between glass, stainless steel, and disposable bags. The objective of a transfer is to have as little change as possible. In this example, the disposable bags showed similar results to the glass container of the donor organization. To mitigate risk, the receiver organization, therefore, used disposable bags and not stainless steel.



instructions must be completed. In-process and release specifications of the product must be adhered to and be comparable with the design space (i.e., the tolerance levels for specific parameters that still guarantee product quality). For the CDMO, every transfer must result in as little change as possible in order to use the existing data and simplify the regulatory approval process.

Navigating the roadblocks for successful technology transfers

As previously discussed, many roadblocks to a successful technology transfer exist, many of which commonly occur in the beginning of the transfer. The following examples help to illustrate three such situations encountered by a CDMO in technology transfer processes and how they were successfully resolved.

In the first example, based on a paper-based gap analysis, both cleanroom processes were analyzed for preparation of primary packaging materials—washing and siliconization of the glass barrels, the kind of silicone oil and mode of siliconization, number and orientation of glass barrels per container, sterilization etc.—prior to entering the filling line. In this example, two issues were identified, in the existing cleanroom—a high degree of silicone oil droplets in the solution and high variation in break-loose and glide forces. Based on the gap analysis, it was determined that compared to the old cleanroom using a wipe down siliconization technique, a spray siliconization was needed in the new cleanroom.

Switching to spray siliconization required the use of silicone oil with a lower viscosity. By using specific analytical methods, such as reflectometric interference spectroscopy, the silicone oil distribution within the glass barrel was optimized, and the glide force was further analyzed as were the corresponding volumes of silicone oil needed to guarantee the quality and to maintain the functionality of the product produced with the new cleanroom process. Because this change in silicone oil viscosity and in the level of residual silicone oil had regulatory consequences, new stability and compatibility studies had to be submitted and adapted.

In the second example, following the relevant attributes derived from the drug product specification including appearance, particulate matter, impurity, sterility, as well as extractable volume, potential risks around the compounding, mixing, and filtration processes were identified. Although this is not unusual given that additional API is necessary to manufacture more batches, larger compounding equipment was needed. As such, lab trials were undertaken to support the selection of the appropriate operational parameters. Besides the change in volume, there was also a need to analyze pumping parameters because greater volume and implemented changes created the need for more time in the filling process and, consequently, in holding times. As a precaution, the filling operation took place under nitrogen pressure to minimize any potential interaction with oxygen. The degree of oxygen sensitivity in the head space of syringes is in most cases not known, thus not defined as a specification. To maintain the current level of oxygen, additional engineering runs in both cleanrooms were required to compare the efficacy of the nitrogen flush. At the end, a modification of the new filling line was required to achieve the required low oxygen level. Although engineering runs have the disadvantage of additional cost and time, as well as a higher consumption of material, their benefits are many and include gaining a greater process understanding and performance while simultaneously training personnel in operations that take place in cleanroom conditions, the demonstration of product comparability, and the verification of CQAs, among others. Further, the risk mitigation efforts can be demonstrated, and any issue or manufacturing instruction can be improved. In this example, the measures to ensure equal product quality ultimately involved the partial reconstruction of a station in the filling line to improve the nitrogen flush.

FIGURE 1 IS COURTESY OF THE AUTHOR.

The third example involved the compounding process. In this example, there existed an incompatibility between the donor organization, which used only glass material, and the receiver organization, which used a disposable bag and stainless-steel container instead of glass. Without knowing the impact on the product given a change in the material, a compatibility lab trial had to be initiated to determine the selection of the appropriate material, in this case, the use of disposable bags; results are shown in **Figure 1**, where it was observed that disposable bags had similar outcomes compared with the glass container from the donor organization.

Knowing the right people

Technology transfer can only be considered successful if the receiving unit can reproduce the transferred product, process, or method against a predefined set of specifications as agreed with the sending unit of the drug. To achieve this level, a project is largely dependent on the skill and performance of individuals assigned to the project, as well as on the experience of the transferring team. The experience of the receiving unit in terms of the drug product, primary packaging, process, and components is extremely important as the initial gap analysis is paper based. Further documentation is a key element of technology transfer, enabling consistent and controlled procedures for technology transfer and to run the process. Clear documentation should provide assurance of process and product knowledge.

Finally, when choosing a CDMO as an outsourcing partner, one must ensure that the company offers a detailed gap analysis for your transfer and can offer significant experience and analytical methods for process design and development. The execution of risk analysis requires experts to identify the relevant degree of detail; therefore, it is important that the appropriate individuals are involved from the start.

Reference

1. ICH Q8, *Pharmaceutical Development* (Geneva, August 2009). **PT**

HPAPI Classification — *contin. from page s20*

Three orders of magnitude difference in acceptable exposure risk can represent a major difference in cost. If an API is placed in a higher OEB in the absence of data and with a large weight placed on uncertainty factors, then far more costly containment will have to be employed, and the manufacturing process will take longer. How necessary is it that the API is treated as so much more hazardous? And what about the intermediates involved in its production? It is less likely that there will be a calculated OEL for those intermediates.

It is important to carefully consider exposure modifiers. Is the process likely to generate dust? If so, the likelihood of airborne hazard is far greater. How long will the operator be exposed to the material? Theoretical OELs are based on an eight-hour exposure; however, the time of potential exposure may be only a few minutes. A case-by-case assessment of the actual facility, process, and procedures will give a far more realistic picture of the hazard. There may be limits on how long people can work on individual projects because of the potential for chronic effects. If an API is a known teratogen, it may be advisable for pregnant women to keep well away.

Determining OEBs

Occupational exposure bands are a useful tool for matching a hazard with containment requirements. APIs that fall into OEB1 are non-toxic, and a standard exposure level of 500 µg/m^3 will suffice. OEB2 compounds will have special hazards, such as carcinogenicity, and the OEL will need to be lower.

At OEB3, where the hazards are greater but not extreme, the opportunity to customize handling to account for real-world situations is greater; this is where the greatest cost and time savings might be anticipated. Here, the containment could—and should—be designed around the process itself. The existing plant may suffice; alternatively, safety requirements might be met by introducing high-efficiency particulate air (HEPA) filters or soft-sided isolators, a more conservative approach than simply using personal protective equipment. The risk assessment should also consider the solvents and whether they can degrade processing or containment equipment. A program of surrogate testing is required to prove that the containment strategy is appropriate and working successfully before the hazardous material is introduced.

OEB4 APIs are more highly potent and toxic, and special handling and careful containment will be required. An additional band, OEB4+, encompasses compounds that are so potent that their OEL falls below 0.1 µg/m^3. For OEB4 and OEB4+ compounds, the opportunity for customization is limited, and the process must be designed around the containment, and not the other way around. Dedicated isolators will most likely be employed, and rapid transfer ports for APIs deemed to be OEB4+.

This type of complete containment is extremely expensive, and while the conservative approach would be to use such containment for all highly potent compounds, in reality it may be overkill for OEB3 APIs. Instead, it may be more realistic to start out with the assumption that full containment is required, but then relax the handling requirements as further data become available, if the data suggest this will be safe. This level of flexibility will allow a CMO to offer its customers a more cost-effective solution, and faster timelines. **PT**

CMO Roundup: Expansions for Biomanufacturing

Feliza Mirasol

I3D/SHUTTERSTOCK.COM

CMOs have been active over the past year in expanding their biologics production and capabilities.

From boosting cell-culture capability to growing bioreactor capacity, contract manufacturing organizations (CMOs) have been making investments to expand biologic output. *Pharmaceutical Technology* highlights some of the major biologics-based CMO activity in the past months.

Acquisitions

In March 2018, Fujifilm acquired Irvine Scientific Sales Company and IS Japan, both cell-culture media companies, in a stock purchase agreement valued at around $800 million. The acquisition expanded Fujifilm's biopharmaceuticals product portfolio to include *in-vitro* fertilization and cell therapy. The company stated that the acquisitions will expand its biopharmaceuticals contract development and manufacturing business and accelerate regenerative-medicine R&D as well as expand its reagent business. The company also plans to establish a new site in Boston, MA, by March 2019 for marketing products and services that support R&D and new-drug manufacturing (1).

In November 2017, Celonic, a biologics development and manufacturing services provider, acquired a biomanufacturing facility in Heidelberg, Germany, from Glycotope, a clinical-stage immune-oncology company. With the acquisition, Celonic expands its GMP manufacturing assets, including continuous perfusion manufacturing, which the company now offers in addition to fed-batch manufacturing and the ability to scale-up from pilot to commercial-scale production. Combining Glycotope's GlycoExpress human cell-line platform with Celonic's CHOvolution integrated development platform will create custom-tailored expression systems (2).

In October 2017, Lonza Pharm & Biotech acquired a clinical-stage mammalian manufacturing facility in Hayward, CA, from Shire. The 58,000-ft^2 site includes 1000-L and 2000-L single-use bioreactors and associated downstream capabilities and provides added cGMP capacity to supplement existing assets in Lonza's Slough, Berkshire, United Kingdom site (3).

New facilities

Lonza plans to add mid-scale mammalian capacity at its facility in Portsmouth, NH, with the installation of multiple 6000-L bioreactors, the company announced in May 2018. Construction is expected to start in late 2018. The company will also include the addition of multiple cell-therapy suites as part of the expansion. The hybrid facility will house full-suite process analytic technology, multi-variate analysis, and single-use technologies in an existing building and is expected to be operational by late 2018 (4).

Patheon, now a part of Thermo Fisher Scientific, is expanding its biologic drug substance manufacturing capabilities with a $50-million investment by Thermo Fisher into the Patheon Biologics Center of Excellence (COE) for Biological Commercial Manufacturing in St. Louis, MO. The site provides process development, clinical cGMP manufacturing, and commercial manufacturing using fed batch and perfusion processes. The investment, announced in April 2018, includes a 64,000-ft^2 expansion to the existing manufacturing building #2 at the site and will feature Thermo Fisher bioproduction bioreactors, consumables, and factory automation. The expansion will double the site's manufacturing capacity. The expanded site is expected to be operational in 2019 (5).

WuXi Biologics, part of WuXi AppTech, announced a couple of expansion plans in recent months. In April 2018, the company said it plans to invest €325 million (US$381 million) in a new biomanufacturing facility in Mullagharlin, Dundalk, County Louth, Ireland. This new facility will use multiple single-use bioreactors for commercial biomanufacturing and is designed to be able to run continuous bioprocessing. The company intends to install a total of 48,000 L fed-batch and 6,000 L perfusion bioreactor capacity (6).

Prior to that, in March 2018, the company announced that it would install 4000-L custom single run (CSR) disposable bioreactors from ABEC, a provider of integrated process solutions and biopharmaceutical manufacturing services, at its new 30,000-L commercial manufacturing facility in Wuxi City, Jiangsu, China. The 4000-L CSRs will enable scale-up of manufacturing up to 24,000 L (7). The new 500,000-ft^2 Wuxi City facility, in which the company invested $150 million, became fully operational in December 2017. It quintuples the company's existing manufacturing capability and will support the biologics commercial manufacturing pipeline coming from global partners. Following completion of the first phase of construction in September 2016, the facility offers two 1000-L disposable bioreactors for perfusion processes, making it the largest perfusion biomanufacturing facility using disposable bioreactors in Asia, as reported by WuXi Biologics. The facility was later equipped with an additional 14 2000-L disposable bioreactors for fed-batch cell culture (8).

AGC Biologics, a contract development and manufacturing organization (CDMO), is adding a 2000-L single-use bioreactor to its Berkeley, CA, facility and plans to build a new complex that will house the company's headquarters in Bothell, WA. The bioreactor addition at its Berkeley facility will support the company's growing biologics capacity, which has tripled over the past three years. The Berkeley facility uses both single-use and stainless-steel bioreactors for cell-culture manufacturing in scales of 100–3000 L (9). The new 15,000-ft^2 complex to be built at Bothell will provide expansion space for additional manufacturing capacity as well as in-house process development labs and corporate administrative offices. The Bothell expansion will also include a new R&D center dedicated to novel therapeutic protein manufacturing technologies (10). The company announced both these investments in March 2018.

CMO Emergent BioSolutions is equipping its bulk manufacturing facility in Bayview, Baltimore, MD, with a 4000-L custom single run (CSR) bioreactor supplied by ABEC, a provider of engineering, equipment, and services to the biopharmaceutical manufacturing sector. The company announced the addition in October 2017. The 4000-L bioreactor, designed specifically for Emergent's process needs, operational requirements, and facility constraints, will expand cell-culture capacity at the Bayview site and is expected to improve process transfer and scale-up, according to ABEC (11).

References

1. Fujifilm, "Fujifilm to Acquire Irvine Scientific Sales Company and IS Japan, Leading Companies of Cell Culture Media," Press Release, March 29, 2018.
2. Celonic, "Celonic Acquires Glycotope's Bio-manufacturing Facility," Press Release, Nov. 3, 2017.
3. Lonza, "Lonza to Acquire a US Clinical Manufacturing Site to Support Ongoing Customer Demand," Press Release, Oct. 3, 2017.
4. Lonza, "Lonza to Invest in Portsmouth, NH (USA) Site, Including Mid-Scale Biologics," Press Release, May 4, 2018.
5. Thermo Fisher Scientific, "Thermo Fisher Scientific Announces $50-Million Investment to Enhance Biologics Capabilities," Press Release, April 23, 2018.
6. WuXi Biologics, "WuXi Biologics to Invest €325-Million to Build Largest Biomanufacturing Facility Using Single-Use Bioreactors in Ireland," Press Release, April 30, 2018.
7. WuXi Biologics, "WuXi Biologics to Install Industry's Largest Single-Use Bioreactor from ABEC at its New Commercial Manufacturing Facility," Press Release, March 20, 2018.
8. WuXi Biologics, "WuXi Biologics Initiated cGMP Manufacturing in the World's Largest Biologics Manufacturing Facility Using Only Single-Use Bioreactors," Press Release, Dec. 6, 2017.
9. AGC Biologics, "AGC Biologics Expands Capacity at Berkeley, California Facility," Press Release, March 6, 2018.
10. AGC Biologics, "AGC Biologics Increases Footprint in Bothell, WA," Press Release, March 29, 2018.
11. ABEC, "ABEC 4,000-Liter Single-Use Bioreactor to Expand Emergent BioSolutions Manufacturing Capability," Press Release, Oct. 24, 2017. **PT**

Small-Molecule Contract Services Update

Amber Lowry

GAJUS/SHUTTERSTOCK.COM

This article provides a sampling of the latest investments, expansions, and acquisitions by small-molecule contract service providers.

Small-molecule contract service providers have advanced their capabilities and offerings to help clients accelerate innovations and tackle industry challenges. This article will explore some recent small-molecule expansions and investments, as well as acquisitions.

New facilities and expansions

In May 2018, Cambrex completed its previously announced pilot plant expansion at its High Point, NC facility (1). The expansion includes the installation and commissioning of a fourth 400-ft^2 reactor suite with two 2000 L glass-lined reactors and a Hastelloy C22 filter dryer, allowing the manufacture of batch sizes ranging from 10–100kg under cGMP conditions for clinical-phase projects. According to a May 15, 2018 company press release, the installation increased the site's reactor capacity by approximately 30%. Additionally, the company upgraded its analytical chromatography data systems for quality control and analytical R&D to Waters' Empower 3 software.

Also in May 2018, Cambrex shared progress on the construction of a $24-million facility at its Charles City plant for the manufacture of highly potent APIs (1). A 4500-ft^2 production area, which will have a reactor capacity of 2200 gallons and manufacture batches from 50–300kg, will operate to an occupational exposure limit down to 0.1µg/m^3. The existing small-scale manufacturing area will be reconfigured, providing a single high-containment building to support early stage development and manufacturing. The company states that the facility is expected to be operational in the first half of 2019.

Cambrex will construct a new 150-m^2 R&D laboratory at its facility in Paullo, Milan, Italy (2). The laboratory will combine chemistry and analytical development capabilities and include 14 fume hoods, glass-lined reactors, and liquid chromatography and gas chromatography systems. In a June 12, 2018 press release, the company reported that construction will be completed by the end of 2018, with installation and validation of instruments to take place in the first quarter of 2019.

The Milan site contains seven production departments, including a pilot plant, kilo-scale plant, and development and analytical laboratories. The company will also recruit additional scientists to increase the number of generic APIs in the company's development portfolio.

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In August 2018, Minakem, the contract development and manufacturing division of Minafin, will open a new, closed-controlled environment, high-containment production facility (3). The new facility, based at the Louvain-la-Neuve plant in Belgium, will extend the company's capacity to develop and manufacture high potency API compounds, such as antibody drug conjugate toxins, from small-scale development to full GMP batch releases. According to the company, this high-class production facility is among only a dozen of its kind in the world; roughly half are located in Europe.

The facility will be equipped with a preparative chromatography system that allows the isolation and purification of target molecules at varying scales (milligrams to hundreds of grams) and suited to addressing a range of needs, from routine activity to analytics. Equipment includes nine fume hoods and new-generation glove boxes dedicated to dry powder handling and weighing, air locks, high efficiency particulate arresting air filters, and cascading flow. Minakem's HPAPI production will be carried out with an occupational exposure limit below 0.1 µg/m3/8h. Operations in the new high-containment facility will begin in September 2018.

Acquisitions

Catalent has agreed to acquire Juniper Pharmaceuticals to expand Catalent's formulation development, bioavailability, and clinical-scale oral dose manufacturing services (4). The acquisition would also include Juniper's Nottingham, UK-based Juniper Pharma Services division.

Catalent states that Juniper's expertise in formulation development and supply will strengthen Catalent's portfolio of solid-state screening, preformulation, formulation, analytical, and bioavailability capabilities including development of spray-dried dispersions, with integrated development, analytical, and clinical manufacturing at the Nottingham facility.

Under the agreement, announced in a July 3, 2018 press release, a subsidiary of Catalent will commence a tender offer to purchase all of Juniper's shares for a price of $11.50, net to the seller in cash. Following the tender offer, Catalent plans to acquire the remainder of the Juniper shares at the same price through a merger with a newly formed wholly owned subsidiary of Catalent. The acquisition is subject to certain customary closing conditions and is expected to close in the first quarter of Catalent's 2019 fiscal year, which Catalent states began on July 1, 2018.

Juniper provides bioavailability enhancement for poorly soluble compounds, including nano-milling, spray drying, hot-melt extrusion, lipid-based drug delivery, as well as cGMP clinical manufacturing for potent and controlled substances. Catalent will continue to support Juniper's Crinone (progesterone gel) franchise marketed by Merck KGaA outside of the United States. Catalent also announced that the Nottingham facility will provide similar capabilities at its centers of excellence for early drug development in San Diego, CA and Somerset, NJ.

Recipharm is set to expand its presence in the respiratory drug market with the acquisition of Sanofi's Holmes Chapel manufacturing site in Cheshire, UK, for £45 million (US$59 million) (5).

The 125,000-m^2 facility manufactures metered-dose inhalers and nasal sprays and develops dry-powder inhalation technologies. The site's 450 employees will transfer to Recipharm, according to the company. The transaction is expected to close in the fourth quarter of 2018.

The acquisition provides Recipharm with additional inhalation commercial drug product manufacturing capabilities, adding to services already offered by Recipharm's inhalation development facility in the US, as stated by the company in a June 13, 2018 press release. Sanofi has also entered into a long-term supply agreement for the products currently manufactured at the facility.

In July 2018, Cambrex announced it entered into a definitive agreement to acquire dosage form contract development and manufacturing organization (CDMO) Halo Pharma for approximately $425 million in total cash consideration (6). The acquisition will be funded with a combination of cash on hand and borrowings against Cambrex's $500-million senior credit facility. Completion of the transaction is subject to customary closing conditions and is expected to occur during the third quarter of 2018.

With the acquisition of Halo, Cambrex will enter the finished dosage form CDMO market. Halo provides drug product development and commercial manufacturing services, specializing in oral solids, liquids, creams, sterile, and non-sterile ointments. Halo's core capabilities include developing and manufacturing highly complex and difficult-to-produce formulations, products for pediatric indications, and controlled substances.

Halo operates two state-of-the-art, GMP-compliant facilities located in Whippany, NJ, and Montreal, Québec, Canada, comprising of 430,000 ft^2 of plant space. Cambrex reports that Halo is currently engaged in more than 100 product development projects for over 70 customers and is expected to generate over $100 million in annual revenue in 2018. The release also states that Halo's 450 employees will join Cambrex's 1200 employees across the US and Europe.

References

1. Cambrex, "Cambrex Completes Pilot Plant Expansion at its High Point, NC Facility," Press Release, May 15, 2018.
2. Cambrex, "Cambrex Expands Generic API Research and Development Capabilities at Milan, Italy Site," Press Release, June 12, 2018.
3. Minakem, "Minakem Opens New High Containment Facility for Production of the Highest Class of HPAPI," Press Release, June 19, 2018.
4. Catalent, "Catalent Signs Agreement to Acquire Juniper Pharmaceuticals, Inc.," Press Release, July 3, 2018.
5. Recipharm, "Recipharm Expands Inhalation Capabilities with GBP 45 Million Acquisition of Sanofi CMO Business Located in UK," Press Release, June 13, 2018.
6. Cambrex, "Cambrex to Acquire Halo Pharma, Adding Drug Development and Finished Dosage Capabilities to Global API Manufacturing Network," Press Release, July 23, 2018. **PT**

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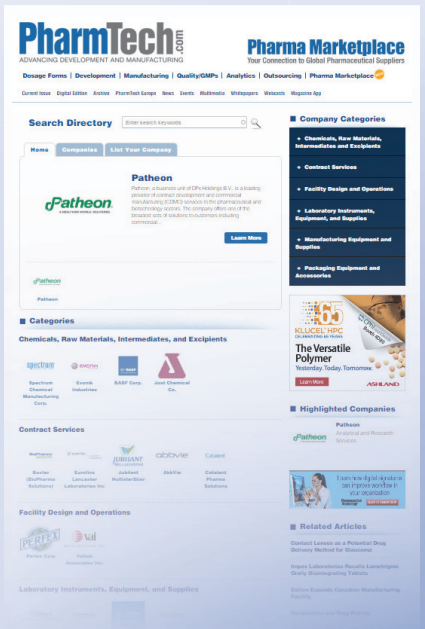

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OUTSOURCING SERVICES

Analytical services: Bioanalytical testing; Chemistry & stability; Microbiology; Product characterization.
Biomanufacturing: Vaccines.
Consulting services: Regulatory, validation, IT, and QA/QC services.

Charles River

3 Chelsea Pkwy Ste 305
Boothwyn, PA 19061 USA
Tel: 610-485-4270
Fax: 610-485-5933
Website: www.qspharma.com
Business Unit Head: Jack Milligan, Sr Dir Bus Dev
Sales Contact: Jack Milligan
Year Founded: 2002
Number of Employees: 26-50
Annual Revenues: $10-25 million

OUTSOURCING SERVICES

Analytical services: Chemistry & stability; Microbiology; Particle characterization; Product characterization.
Commercial manufacturing: High-potency or high-containment manufacturing (finished drug product); 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.
Packaging & logistics: Clinical packaging & distribution.

See our ad on page s29

Chemic Labs

480 Neponset St Bldg 7
Canton, MA 02021 USA
Tel: 781-821-5600
Fax: 781-821-5651
Email: lcw@chemiclabs.com
Website: www.chemiclabs.com
Business Unit Head: Joseph St. Laurent, CSO/Pres
Sales Contact: Joseph St. Laurent
Year Founded: 1998
Number of Employees: 26-50

OUTSOURCING SERVICES

Analytical services: Bioanalytical testing; Chemistry & stability; Product characterization.
Commercial manufacturing: Active Pharmaceutical Ingredients (API) manufacturing - (cGMP, large molecules/biologics); Specialty dosage forms (inhalation/nasal, transdermal, other) .
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) - small molecule; Other delivery forms (transdermal, inhalable...); Solid dose, semi-solids & liquids development.

Chemical Solutions Ltd

931 N 7th St
Harrisburg, PA 17102 USA
Tel: 717-697-7536
Fax: 717-697-4800
Email: amcintyre@chemicalsolutionsltd.com
Website: www.chemicalsolutionsltd.com
Business Unit Head: Brian LaBine, Pres
Sales Contact: Alyssa McIntyre
Year Founded: 1997
Number of Employees: 26-50
Annual Revenues: $0-10 million

OUTSOURCING SERVICES

Analytical services: Chemistry & stability.

See our ad on page s2

CMIC CMO USA Corp

Cedar Brook Corporate Center, 3 Cedar Brook Dr
Cranbury, NJ 08512 USA
Tel: 609-395-9700
Email: bd@cmiccmousa.com
Website: www.cmiccmousa.com
Business Unit Head: Yasuhiro Sejima, Exec VP & Gen Mgr
Sales Contact: Maureen Bell
Year Founded: 2007
Number of Employees: 51-100
Annual Revenues: $10-25 million

OUTSOURCING SERVICES

Analytical services: Chemistry & stability.
Commercial manufacturing: Ingredient processing (milling, coating, etc.); Solid dose manufacturing.

See our ad on page s5

Coating Place

200 Paoli St
PO Box 930310
Verona, WI 53593 USA
Tel: 608-845-9521
Fax: 608-845-9526
Email: info@coatingplace.com
Website: www.coatingplace.com
Business Unit Head: Timothy Breunig, Pres & CEO
Sales Contact: Corey Uselman
Year Founded: 1976
Number of Employees: 101-250
Annual Revenues: $25-50 million

OUTSOURCING SERVICES

Commercial manufacturing: Ingredient processing (milling, coating, etc.); Semi-solids & liquid manufacturing; Solid dose manufacturing.

Dalton Pharma Services

349 Wildcat Rd
Toronto, Ontario M3J 2S3 Canada
Tel: 416-661-2102
Email: pm@dalton.com
Business Unit Head: Peter Pekos
Sales Contact: ckotoris@dalton.com
Number of Employees: 101-250

OUTSOURCING SERVICES

Analytical services: Bioanalytical testing; Chemistry & stability; Microbiology; Particle characterization; Product characterization.
API and advanced intermediates (cGMP, small molecule) manufacturing capabilities: Acid chlorides; Acylation; Amidation; Amino acids and analogs; Biocatalytsis; Borane chemistry; Bromine chemistry/bromination; Carbohydrate chemistry; Chemocatalysis; Heterocyclic chemistry; Lithium chemistry; Organometallic chemistry; Sulfonation.
Biomanufacturing: Vaccines.
Commercial manufacturing: Active Pharmaceutical Ingredients (API) and advanced intermediates manufacturing (cGMP, small molecule); Active Pharmaceutical Ingredients (API) manufacturing - (cGMP, large molecules/biologics); Ingredient processing (milling, coating, etc.); Parenteral drug manufacturing (Injectables, etc.); Semi-solids & liquid manufacturing; Solid dose manufacturing.
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; Injectable products development; Solid dose, semi-solids & liquids development.
Packaging & logistics: Clinical labels; Clinical packaging & distribution.

EAG LABORATORIES | WE KNOW HOW

See our ad on Cover Tip, pages s10, s11

EAG Labs

4780 Discovery Dr
Columbia, MO 65201 USA
Tel: 800-538-5227
Business Unit Head: Amanda Halford, EVP Life Sciences
Sales Contact: Eric Hoffman,
Number of Employees: 501+
Annual Revenues: $100-250 million

OUTSOURCING SERVICES

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

eurofins | Lancaster Laboratories

See our ad on pages s16, s17

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.

EuTech Scientific Services

810 N 2nd Ave
Highland Park, NJ 08904 USA
Tel: 732-249-1600/800-284-9245
Fax: 732-249-2806
Email: custserv@eutechsci.com
Website: www.eutechsci.com
Business Unit Head: custserv@eutechsci.com
Sales Contact: custserv@eutechsci.com
Year Founded: 1994
Number of Employees: 1-25

OUTSOURCING SERVICES

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

Exova

9240 Santa Fe Springs Rd
Santa Fe Springs, CA 90670-2618 USA
Tel: 562-948-2225
Fax: 562-948-5850
Email: info400@exova.com
Website: www.exova.com
Business Unit Head: Eric Lindsay, Gen Mgr
Sales Contact: Louis Albanese
Year Founded: 1984
Number of Employees: 51-100
Annual Revenues: $10-25 million

OUTSOURCING SERVICES

Analytical services: Bioanalytical testing; Chemistry & stability.

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
Business Unit Head: Jean-Francois Paquin, Operations Dir
Year Founded: 1988
Number of Employees: 26-50

OUTSOURCING SERVICES

Packaging & logistics: Commercial packaging.

Galbraith Labs

2323 Sycamore Dr
PO Box 51610 (37950)
Knoxville, TN 37921-1700 USA
Tel: 865-546-1335/877-449-8797
Fax: 865-546-7209
Email: labinfo@galbraith.com
Website: www.galbraith.com
Business Unit Head: Salvador Pastor, Bus Dev Mgr
Year Founded: 1950
Number of Employees: 51-100
Annual Revenues: $0-10 million

OUTSOURCING SERVICES

Analytical services: Chemistry & stability; Product characterization.

Gibraltar Labs

122 Fairfield Rd
Fairfield, NJ 07004 USA
Tel: 973-227-6882/877-315-5847
Fax: 973-227-0812
Email: kkohan@gibraltarlabsinc.com
Website: www.gibraltarlabsinc.com
Sales Contact: Kristah Kohan
Year Founded: 1970
Number of Employees: 51-100

OUTSOURCING SERVICES

Analytical services: Chemistry & stability; Microbiology.

Grifols Intl, S.A.

Parc Empresarial Can Sant Joan
Av. de la Generalitat, 152
Sant Cugat del Vallès, Barcelona 08174 Spain
Tel: +34935712199
Email: partnership@grifols.com
Website: www.partnership.grifols.com
Number of Employees: 501+
Annual Revenues: $500 million+

OUTSOURCING SERVICES

Commercial manufacturing: Parenteral drug manufacturing (Injectables, etc.).

See our ad on page s25

Halo Pharmaceutical

30 N Jefferson Rd
Whippany, NJ 07981 USA
Tel: 973-428-4000
Fax: 973-428-4017
Email: services@halopharma.com
Website: www.halopharma.com
Business Unit Head: Lee Karras, CEO
Sales Contact: Lee Karras, CEO
Year Founded: 2008
Number of Employees: 251-500
Annual Revenues: $50-100 million

OUTSOURCING SERVICES

Analytical services: Microbiology; Product characterization.
Commercial manufacturing: Semi-solids & liquid manufacturing; Solid dose manufacturing.
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Solid dose, semi-solids & liquids development.
Packaging & logistics: Commercial packaging.

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: Lynn Allen
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 s13

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.

See our ad on page s7

Mikart

1750 Chattahoochee Ave
Atlanta, GA 30318 USA
Tel: 404-351-4510/888-4-MIKART
Fax: 404-350-0432
Email: sales@mikart.com
Website: www.mikart.com
Business Unit Head: Blair Jones, VP Sls & Mktg
Sales Contact: Blair Jones
Year Founded: 1975
Number of Employees: 101-250

OUTSOURCING SERVICES

Analytical services: Chemistry & stability.
Commercial manufacturing: Semi-solids & liquid manufacturing; Solid dose manufacturing.

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

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: $25-50 million

OUTSOURCING SERVICES

Analytical services: Chemistry & stability; Microbiology; Product characterization.

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
Number of Employees: 26-50
Annual Revenues: $0-10 million

OUTSOURCING SERVICES

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

Perritt Labs

145 S Main St
PO Box 147
Hightstown, NJ 08520-3341 USA
Tel: 609-443-4848
Fax: 609-443-5293
Email: jtrepper@perrittlab.com
Website: www.perritt.com
Business Unit Head: John Trepper, VP, Bus Dev
Sales Contact: John Trepper
Year Founded: 1973
Number of Employees: 26-50

OUTSOURCING SERVICES

Analytical services: Microbiology.

Pharm Ops

101 Broad St
Phillipsburg, NJ 08865-1208 USA
Tel: 908-454-7733
Fax: 908-454-8542
Email: info@pharmops.com
Website: www.pharmops.com
Business Unit Head: Nkere Ebube, Pres
Year Founded: 2015
Number of Employees: 1-25

OUTSOURCING SERVICES

Analytical services: Bioanalytical testing; Chemistry & stability; Microbiology; Particle characterization; Product characterization.
Commercial manufacturing: Semi-solids & liquid manufacturing; Solid dose manufacturing.
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Active Pharmaceutical Ingredients (API) - small molecule; Injectable products development; Solid dose, semi-solids & liquids development.

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.

See our ad on page s9

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, PhD
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.

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.

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
Business Unit Head: Jeffrey Worthington, Pres
Sales Contact: David Tisi
Year Founded: 2006
Number of Employees: 1-25

OUTSOURCING SERVICES

Analytical services: Product characterization.
Consulting services: Project & sourcing management services.

TGA Sciences

47 Hall St
Medford, MA 02155 USA
Tel: 781-393-6910
Fax: 781-393-6894
Email: msettles@tgasciences.com
Website: www.tgasciences.com
Number of Employees: 1-25
Annual Revenues: $0-10 million

OUTSOURCING SERVICES

Analytical services: Bioanalytical testing.
Biomanufacturing: Cell culture.

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
Number of Employees: 51-100
Annual Revenues: $10-25 million

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

46701 N Commerce Center Dr
Plymouth, MI 48170 USA
Tel: 734-545-0696
Email: gerry.cox@velescopharma.com
Website: www.velescopharma.com

OUTSOURCING SERVICES

Analytical services: Chemistry & stability; Product characterization.
Consulting services: Regulatory, validation, IT, and QA/QC services.
Formulation Development & Phase I/II Clinical Trial Materials (CTM): Solid dose, semi-solids & liquids development.
Packaging & logistics: Clinical labels; Clinical packaging & distribution.

See our ad on page s37

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.

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Fast Locator Index™
North America

	Analytical services					Bio-manufacturing						Consulting				Commercial manufacturing									Development and Phase I/II CTM					Packaging and logistics		
	Bioanalytical testing	Chemistry & stability	Microbiology	Particle characterization	Product characterization	Cell culture	Microbial fermentation	Microbial manufacturing	Nucleic acids	Stem cell production	Vaccines	Equipment services	Investment recovery	Project and sourcing management services	Regulatory, validation, IT, and QA/QC services	Surplus asset management	API & advanced intermediates (cGMP small molecules)*	API (cGMP, large molecules/biologics)	High-potency or high-containment manufacturing	Ingredient processing (milling, coating, etc.)	Parenteral drug manufacturing	Semi-solids & liquids manufacturing	Solid dose manufacturing	Specialty dosage forms	API-small molecule	API-large molecule/biologics	Injectable products development	Solid dose, semi-solids, & liquids development	Other delivery forms (transdermal, inhalable)	Clinical labels	Clinical packaging and distribution	Commercial packaging
Almac Group	✓	✓		✓	✓												✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ASM Aerosol-Service AG		✓												✓	✓							✓		✓				✓				✓
Avista Pharma Solutions	✓	✓	✓	✓	✓	✓	✓	✓									✓	✓	✓		✓	✓	✓		✓	✓	✓	✓		✓	✓	✓
Baxter (BioPharma Solutions)	✓	✓	✓	✓	✓						✓			✓	✓		✓	✓	✓		✓				✓	✓	✓					✓
Butterworth Labs Ltd		✓			✓																											
Charles River	✓	✓	✓		✓						✓				✓																	
Charles River		✓	✓	✓	✓														✓			✓	✓	✓	✓					✓	
Chemic Labs	✓	✓			✓									✓	✓			✓						✓	✓			✓	✓			
Chemical Solutions Ltd		✓																														
CMIC CMO USA Corp		✓																		✓			✓									
Coating Place																				✓		✓	✓									
Dalton Pharma Services	✓	✓	✓	✓	✓						✓			✓	✓		✓	✓		✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	
EAG Labs	✓	✓		✓	✓	✓																										
Eurofins Lancaster Labs	✓	✓	✓	✓	✓	✓																										
EuTech Scientific Services	✓	✓			✓																											
Exova	✓	✓																														
Fillab																																✓
Galbraith Labs		✓			✓																											
Gibraltar Labs		✓	✓																													
Grifols Intl, S.A.																					✓											
Halo Pharmaceutical			✓		✓																	✓	✓					✓				✓
Jubilant HollisterStier																					✓	✓		✓								
Lonza	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Metrics		✓	✓	✓															✓	✓		✓	✓	✓	✓			✓				
Mikart		✓																				✓	✓					✓			✓	✓
O'Neal														✓																		
Particle Technology Labs Ltd				✓	✓										✓																	
Perritt Labs			✓																													
Pharm Ops	✓	✓	✓	✓	✓																	✓	✓		✓		✓	✓				
Phoenix Equipment Corp												✓	✓																			
Pyramid Laboratories		✓																			✓						✓					
Reed-Lane																																✓
Regis Technologies		✓															✓								✓							
Senopsys					✓									✓																		
TGA Sciences	✓					✓																										
University of Iowa Pharmaceuticals		✓																	✓		✓	✓	✓				✓	✓				
Veltek Associates															✓																	
Wickham Labs Ltd			✓												✓																	

*For Fast Locators of API production technologies, see Page s50

Fast Locator Index™
Europe and Asia

	Analytical services					Bio-manufacturing						Consulting					Commercial manufacturing								Development and Phase I/II CTM					Packaging and logistics		
	Bioanalytical testing	Chemistry & stability	Microbiology	Particle characterization	Product characterization	Cell culture	Microbial fermentation	Microbial manufacturing	Nucleic acids	Stem cell production	Vaccines	Equipment services	Investment recovery	Project and sourcing management services	Regulatory, validation, IT, and QA/QC services	Surplus asset management	API & advanced intermediates (cGMP small molecules)*	API (cGMP, large molecules/biologics)	High-potency or high-containment manufacturing	Ingredient processing (milling, coating, etc.)	Parenteral drug manufacturing	Semi-solids & liquids manufacturing	Solid dose manufacturing	Specialty dosage forms	API-small molecule	API-large molecule/biologics	Injectable products development	Solid dose, semi-solids, & liquids development	Other delivery forms (transdermal, inhalable)	Clinical labels	Clinical packaging and distribution	Commercial packaging
Almac Group	✓	✓		✓	✓												✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ASM Aerosol-Service AG		✓												✓	✓							✓		✓				✓				✓
Avista Pharma Solutions	✓	✓	✓	✓	✓	✓	✓	✓									✓	✓	✓		✓	✓	✓		✓	✓	✓	✓		✓	✓	✓
Baxter (BioPharma Solutions)	✓	✓	✓	✓	✓						✓			✓	✓		✓	✓	✓		✓				✓	✓	✓					✓
Butterworth Labs Ltd		✓			✓																											
Charles River	✓	✓	✓		✓						✓				✓																	
Charles River		✓	✓	✓	✓														✓			✓	✓	✓	✓						✓	
Chemic Labs	✓	✓			✓									✓	✓			✓						✓	✓			✓	✓			
Chemical Solutions Ltd		✓																														
Coating Place																				✓		✓	✓									
Dalton Pharma Services	✓	✓	✓	✓	✓						✓			✓	✓		✓	✓		✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	
EAG Labs	✓	✓		✓	✓	✓																										
Eurofins Lancaster Labs	✓	✓	✓	✓	✓	✓																										
EuTech Scientific Services	✓	✓			✓																											
Exova	✓	✓																														
Fillab																																✓
Galbraith Labs		✓			✓																											
Gibraltar Labs		✓	✓																													
Grifols Intl, S.A.																					✓											
Halo Pharmaceutical			✓		✓																	✓	✓					✓				✓
Jubilant HollisterStier																					✓	✓		✓								
Lonza	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Metrics		✓	✓	✓															✓	✓		✓	✓	✓	✓			✓				
Particle Technology Labs Ltd				✓	✓										✓																	
Pharm Ops	✓	✓	✓	✓	✓																	✓	✓		✓		✓	✓				
Regis Technologies		✓															✓								✓							
Senopsys					✓									✓																		
TGA Sciences	✓					✓																										
Veltek Associates															✓																	
Wickham Labs Ltd			✓												✓																	

*For Fast Locators of API production technologies, see Page s50

	Acetylenic chemistry	Acid chlorides	Acylation	Amidation	Amino acids and analogs	Asymmetric synthesis or chiral chemistry	Azide chemistry	Biocatalysis	Borane chemistry	Bromine chemistry/bromination	Carbohydrate chemistry	Chemocatalysis	Cryogenics (low-temperature reactions)	Cyanide chemistry	Fluorination	Heterocyclic chemistry	Hydrazine chemistry	Lithium chemistry	Nitration	Organometallic chemistry	Phosgenation	Sulfonation
Almac Group							✓															
Avista Pharma Solutions			✓		✓		✓			✓	✓						✓	✓				
Baxter (BioPharma Solutions)					✓																	
Dalton Pharma Services		✓	✓	✓	✓		✓	✓	✓	✓	✓				✓		✓		✓		✓	
Lonza							✓	✓	✓		✓	✓		✓		✓		✓		✓		
Regis Technologies	✓	✓	✓	✓	✓	✓			✓			✓			✓			✓	✓	✓	✓	

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