# Trends in Manufacturing of Specialty Products

## Table of Contents

1. **Pain Medication**
   - FDA and Manufacturers Seek Safer Pain Medications
   - Jill Wechsler
   - Page 3

2. **Handling HPAPIs**
   - Handling HPAPIs: Do Your CMOs Have the Right Stuff?
   - Agnes Shanley
   - Page 8

3. **Minimizing Risk**
   - Minimizing Risk during HPAPI Manufacture
   - Cynthia A. Challener
   - Page 15

4. **Technology Transfer**
   - Planning for Successful Technology Transfer
   - Michael Valazza
   - Page 21

---

This custom eBook is sponsored by Catalent Pharma Solutions and published by Pharmaceutical Technology.
The campaign against opioid abuse opens door to more innovative therapies.

One main goal of FDA’s Opioid Action Plan is to support the development of less dangerous pain medicines, including generic versions of therapies with anti-abuse features. With reports of thousands of opioid-related deaths a year, biopharmaceutical manufacturers are investing in promising non-opioid compounds and other innovations able to manage chronic and acute pain more safely.

These initiatives are supported by FDA’s Opioid Action Plan, released in February 2016, to assure Congress that FDA would do more to ensure the safe use of powerful opioid pain medications. The plan includes broader FDA consultation with advisory committees on the approval of new opioid formulations, stronger boxed warnings on drug labels, and easier access to treatments for opioid overdoses (1). FDA also supports expanded use of painkillers with abuse deterrent formulations (ADFs) through the development of less costly generic versions of these advanced treatments.
The challenge for FDA, manufacturers, and the medical community is to meet the genuine demand from millions of individuals suffering from chronic and acute pain, while also doing more to prevent opioid overdose and misuse. So far, more informative drug labels, prescriber education, and pharmacy monitoring have done little to reduce abuse. Moreover, the new ADFs are expensive and not widely used. Approximately 90% of opioid prescribing is for some 175 immediate-release (IR) products, including more than 100 generics. FDA has approved approximately 35 extended-release/long-acting (ER/LA) therapies and five ER products with abuse deterrent (AD) features, but these more expensive medications comprise only 10% of the market.

The public outcry for action to curb opioid-related addiction and deaths, however, is encouraging innovation and investment in the pain treatment area. The House and Senate have held numerous hearings on this lethal epidemic and are weighing a range of legislative actions to support more rigorous prescription monitoring and expanded treatment options for addicts. One proposal would levy fees on opioid manufacturers related to the strength of their medications to fund substance abuse treatment; another bill would provide added exclusivity and other incentives for industry investment in R&D on safer pain medicines.

The White House has requested an additional $1.1 billion to support local and state treatment programs, to better control opioid prescribing and dispensing, and to increase patient access to addiction treatments buprenorphine and naloxone. One consequence of cracking down on prescription drug abuse, unfortunately, has been a notable increase in the use of heroin and the even more dangerous illegal drug fentanyl.

The Centers for Disease Control and Prevention (CDC) recently issued new guidelines advising physicians to limit opioid prescriptions to three-day supplies for individuals with severe pain that can’t be managed with less dangerous analgesics. Some states are establishing prescribing limits on opioids, and a new Massachusetts law requires manufacturers to collect and dispose of unwanted controlled substances to prevent diversion. States also are filing suits against manufacturers for promoting pain medicines as safe and effective, as seen in a $200,000 fine paid by Endo Pharmaceuticals to New York for allegedly claiming greater safety for the AD features of its Opana ER. The Federal Trade Commission also recently issued a complaint against Endo for using pay-for-delay agreements to block generic competition to Opana (2).
More meetings, stiffer warnings
Meanwhile, FDA has filled its calendar with meetings with outside advisors to consider the regulation and approval of new analgesics, especially those for children. At a March 1, 2016 session of FDA’s Science Board, FDA Commissioner Robert Califf and agency officials sought advice on developing effective pain treatments, including ADFs. FDA’s pediatric advisory committee discussed pediatric development plans for prescription opioids at a meeting in April 2016 and planned to explore the issue in greater depth at a two-day session in September 2016. In May 2016, advisors aimed to review an application for an IR product that claims abuse-deterrent properties. Another meeting that month was slated to examine the effectiveness of the agency’s current Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioids; one issue is whether to extend the program to the much greater number of IR products. And in June 2016, two expert panels planned to jointly weigh applications for two new ER painkillers featuring AD properties.

FDA also has proposed stronger warnings on the labels for all IR opioid products, similar to labeling changes made for ER opioid analgesics in 2013. The updated labeling guidance published in March 2016 includes boxed warnings to heighten prescriber awareness of the high risk of misuse, abuse, overdose, and death associated with these therapies. The revision also cautions women not to take these drugs chronically during pregnancy and calls for both IR and ER painkillers to carry safety information about the risk of drug interactions that can have serious adverse effects. Yet FDA stopped short of setting specific dosing recommendations or maximum doses, despite pressure for prescribing limits from some health authorities.

Seeking innovation
The development of more effective ADFs is considered key to curbing abuse of potent ER/LA products, and FDA encouraged brand manufacturers to take this route in guidance that was finalized in April 2015. The agency has approved five ER opioids with AD features, is evaluating some 30 active investigational new drug applications (INDs) for ADFs and other new technologies, and at least three more products are being considered for approval this year, as noted previously.

But the higher cost of these products has drawn protests from pain patients and payers, prompting support for developing generic ADFs. FDA responded in March 2016 with draft guidance that outlines a “tier-based” approach for generics makers to conduct in-vitro studies and other manipulations to measure a
product’s anti-abuse features (5–6). FDA maintains that generics should meet the same standards for abuse deterrence as innovators and plans to hold a public meeting on the proposal after considering comments that were due in late May 2016.

Despite these efforts, it may be years before generic ADFs come to market due to long patent protections for these relatively new brand products, and successful generic versions won’t be cheap. The testing and development of all pain medications is difficult, and ADFs are even more challenging. At the Science Board meeting, FDA staffers explained that just two out of 100 clinical trials for pain medications get past Phase II due to limited nonclinical models and challenges in pain measurement.

FDA looks to collaborate more with academics, advocacy groups, and industry to identify new AD technologies and drug-delivery systems that can slow penetration or bind to different receptors. A number of biotech manufacturers are exploring such strategies, including Baltimore-based Centrexion Therapeutics, which announced progress in developing non-opioid pain therapies (7). Headed by former Pfizer chairman Jeffrey Kindler and former Celgene chief Sol Barer, Centrexion made waves by acquiring three experimental pain compounds from Boehringer Ingelheim and announcing further clinical trials for an injectable, synthetic capsaicin to treat chronic osteoarthritis knee pain. Such efforts to create safer pain medications are likely to benefit from regulatory and financial support.

References
flexible manufacturing. 
custom solutions. 
reliably supplied.

20 GLOBAL MANUFACTURING SITES 
with $1B+ invested in capacity and capability over the last 5 years

80+  YEARS OF EXPERTISE 
Product development to 
commercial manufacturing

500  NEW PRODUCTS IN 
DEVELOPMENT 
165+ launched annually

70B+  DOSES MANUFACTURED 
ANNUALLY

TECHNOLOGY TRANSFERS & LAUNCHES 
Proven track record of product launches in multiple markets, with the analytical, development, project management, regulatory and operational expertise to support successful technology transfer at any phase of the development cycle.

CUSTOM SUITES & SCALABLE SOLUTIONS 
Global infrastructure and business models to provide unique manufacturing solutions. Flexibility to design dedicated suites, and scalable capacity and integrated services to support small orphan programs through to large network rationalization strategies.

SPECIALIZED HANDLING & TECHNOLOGIES 
Expertise in manufacturing technologies to improve efficiency, reliability, and safety, packaging technologies for serialization, and special handling experience across +300 potent, cytotoxic, hormonal and controlled substances.
HANDLING HPAPIs: DO YOUR CMOs HAVE THE RIGHT STUFF?

Agnes Shanley

Ignoring a contract partner’s ability to handle highly potent APIs (HPAPIs) safely may have serious consequences. Drug owners and contract service providers alike must understand the complexities and liabilities involved in working with HPAPIs.

Highly active or potent pharmaceutical ingredients (HPAPIs) comprise different compounds, but share one deadly characteristic: the potential to inhibit production of specific enzymes and cause cancer, mutations, development effects, or sickness, at very low doses, in those exposed to them.

Currently, there are no specific occupational health, safety, and environmental protection regulations covering HPAPIs. In the United States, the Occupational Health and Safety Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), and the US Environmental Protection Agency (EPA) have
limited specific requirements for potent compound handling in healthcare and manufacturing settings.

Industry groups in the United States and Europe have developed health risk-based approaches for setting occupational exposure limits (OELs) in such areas as cleaning validation, by setting permitted or acceptable daily exposure limits (PDEs or ADEs), to address carryover of any residual HPAPI. The result has been the International Society for Pharmaceutical Engineers’ (ISPE) RiskMapp baseline guidance, and the European Medicines Agency’s (EMA) guidance for preventing cross-contamination.

Drug manufacturers are developing more potent drugs, and despite the lack of specific environmental and safety regulations, HPAPIs have become fertile ground for contract manufacturing and contract development and manufacturing organizations (CMOs and CDMOs), which have been actively building up capacity over the past few years. Experts warn, however, that a systematic and scientific approach is needed. Simply having containment equipment and basic procedures will not be enough to ensure safety.

Typically, large pharmaceutical companies have the industrial hygienists and occupational toxicologists on staff to evaluate the potential risks of any new HPAPI, and to conduct the necessary safety assessments. Smaller companies and CDMOs/CMOs may not have those experts on staff. Teams that visit potential contract partners may be so focused on cGMPs and product specs that they overlook questions of worker safety and environmental risk from exposure to HPAPIs.

In addition, CDMOs/CMOs may not have done a sufficiently thorough assessment to determine whether they can handle a potent new drug safely. Failure to vet potential partners thoroughly can lead to regulatory problems with OSHA and potential legal liability.

SafeBridge Consultants, based in Mountain View, CA, established a third-party certification program 15+ years ago, which assesses a manufacturer’s HPAPI handling and manufacturing program readiness. The program focuses on four areas: management systems, evaluating hazards and risks, assessing engineering controls, and analyzing training and standard operating procedures (SOPs). The process also reviews such tools as OELs, industrial hygiene sampling, and analytical work. In addition, it scrutinizes containment and controls, and assesses potential environmental impact. The company has already certified a number of pharma CDMOs.

SafeBridge Consultants’ roots go back to Syntex Corp., which helped establish
the “control banding” approach that is used in industrial hygiene to determine the potential risk of exposure to new APIs for which no exposure data exist. Pharmaceutical Technology spoke with SafeBridge Consultants’ founder and CEO John Farris and cofounder, vice-president and principal toxicologist Allan Ader, to discuss best practices for sponsors and CMOs alike.

**The certification process**

**PharmTech:** Why did you decide to go into business?

**Farris:** With the rise of contract manufacturing in pharma, we saw the need to come up with a metric that could evaluate companies’ capabilities to conduct potent compound operations safely to minimize exposure. We had developed a tool while at Syntex to look at the industrial hygiene of our internal facilities around the world. We modified that to come up with a measurement tool for potent-drug safety that would work for any contractor and that anyone could use. It’s a weighted 60-plus criteria exercise that has been proven to be effective and objective in evaluating capabilities.

A CMO can use certification to show clients that they are competent in HPAPI manufacturing and handling. We also offer a “gap assessment” or qualitative approach that can allow companies to measure their own performance using the same criteria.

**PharmTech:** How do companies apply for certification?

**Farris:** We start with a precertification review, where we send a person to take a walk through the plant, look at procedures and give the company a candid idea of whether or not they have a chance of passing. If they pass the first hurdle, we send two professionals out to do a two-day review (up to three days for companies outside of the United States).

We don’t certify new facilities because they haven’t had enough significant run time. They won’t have the data that we ask for to support the certification, and they haven’t proven that they can work consistently within industry best practices.

**PharmTech:** What other data do you need?

**Ader:** There are two key points: toxicology evaluations of hazards and materials you will handle, then the industrial hygiene studies measuring impact on workers, and the air and surface monitoring studies to show that you are containing materials and maintaining safe levels. In addition, you need to show that you repeat studies to prove that you are doing this accurately.
and consistently with industry best practices.

**PharmTech:** How long does the certification last?

**Farris:** For the US and Europe, certification lasts for two years. During the off year, the company must do a self-assessment and share results with us. For companies in Asia, recertification is required every year.

**Current practices**

**PharmTech:** Do you think that pharmaceutical companies are lax in their handling of potent compounds?

**Farris:** They want to do things right but they don’t know how involved it can be. Historically, Big Pharma has struggled with potent drug safety, and, despite its efforts, over the years it has had incidents of exposure to workers. Now, these are the companies with significant resources in toxicology and industrial hygiene that are applying their skills to prevent this. If Big Pharma has trouble, imagine what a small CMO or innovator company faces.

**Ader:** You have to be able to recognize, evaluate, and control the hazard. These are the three basic principles of industrial hygiene and toxicology. CMOs or smaller companies may have some, but not all, bases covered. For instance, they might do a good job of hazard evaluation, but not air monitoring. Sometimes, the gaps boil down to cost issues. If you’re thinking of building isolators for all your process steps, that will involve significant cost, and some might try another option that, in the end, won’t be sufficient protection for that particular compound. The evaluation by toxicologists and developing acceptable limits or appropriate occupational health categories, or bands, is key. Sometimes, that step gets missed.

**Farris:** Another problem is that, when smaller companies do invest in expensive and high-tech controls like isolators, some of them then figure that the job is done and they’re good to go. They fail to recognize the fact that, if you don’t measure performance, you can’t guarantee safety.

With HPAPIs, you can’t tell there’s a problem just by looking. You need to measure performance. Safe levels for some of these drugs are down in the range of nanograms per cubic meter of air, 1,000 times below what you can see in air at a minimum for some of these compounds.

You can’t tell whether the isolator is leaking unless you have a catastrophic failure. If you don’t measure its performance, you won’t know if you might have a slow and potentially continuous
leak and exposure. You might also pass things out of the isolator that have particulates on them and can cause exposure, and have “drag out” of a room or isolator into a clean area. You won’t know if you don’t measure.

PharmTech: Because OSHA does not offer specific guidance on HPAPIs, could companies have exposure problems and could workers be affected without knowing it?

Farris: OSHA and NIOSH have published guidance on hazardous drugs, but it is intended for the healthcare industry, not for manufacturing and R&D. OSHA will get involved if an employee gets sick, and will investigate the facility. OSHA has come in and cited companies, but it’s always after the fact. There are both acute and chronic hazards. OSHA gets involved mainly in acute incidents, when workers develop a rash or symptoms from acute high exposures, or reproductive health issues.

Problem areas
PharmTech: What are the top issues and questions that companies fail to consider when they are dealing with potent ingredients, both sponsors and CMOS?

Ader: Generally, there are three problem areas. They don’t have toxicology support, and if they have the toxicology support they don’t have an understanding of the pharmaceutical substance’s unique potencies and toxicities.

They haven’t run adequate industrial hygiene studies prior to startup (conducting surrogate studies on containment equipment before actual production begins), during initial production batches, and then, periodically after startup, to verify the performance of control systems.

The third, and biggest problem, is that they often don’t know what they can and can’t handle. They need to assess the capability of their equipment and facility. That is very closely related to the industrial hygiene data that they need to gather. Some companies do industrial hygiene studies with only two samples. That cannot adequately assess health risk. Studies must be scientifically supportable and use statistics in order to determine systems capability and verify performance.

Farris: You need to understand what you can and can’t handle and why, and be able to articulate that to customers. This also gives you a focus for improvement. If you want to handle the ultra-potent materials, but you know you don’t have adequate controls in place, you can then budget and plan to improve those areas so that you can grow your business.
Qualifying contract service providers

**PharmTech:** Who should go to evaluate a CMO that’s working with HPAPiS?

**Ader:** Typically, pharma companies send the quality people or the formulation or process chemists who are transferring the process over to the CMO. They’re looking at timing, whether the CMO can produce to the specs that they’re trying to achieve, whether they can perform this specific reaction, or make this particular formulation as they did inhouse. They’re focused on timing and the bottom line.

Then, way down at the bottom of the list of specs, is the question of whether or not they can handle HPAPiS.

**Farris:** Only Big Pharma companies typically send environmental health and safety professionals out to review third parties.

**Ader:** Usually, the industrial hygienist is the key person, since he or she will do the exposure assessment.

**PharmTech:** What issues are posed by new compounds?

**Farris:** We’re one of the innovators, with several other companies back in the late 1980s, of the occupational-health categorization system, or control banding, where we group compounds based on toxicity and potency. We use this approach when there isn’t a lot of data and you can’t determine OELs quantitatively. Many companies use those numbers alone. But we have linked them to best handling practice, which is important. It’s really a hand and glove, with the hand being toxicity evaluation and assessment, and the glove, the handling practice and work-environment descriptors that will allow you to make the compound safely.

The cleaning validation question

**PharmTech:** How does this fit in with cleaning validation?

**Ader:** This is where the quality and occupational health aspects merge, because they both should employ some level of quantitative risk assessment. Historically, in cleaning validation, you can have carryover to the next product. Previously, you could establish a cleaning limit based on arbitrary cutoffs, such as 10 ppm, or 1/10,000 of LD-50, or half the lethal dose in rats.

These arbitrary approaches don’t use the most current risk assessment approaches to determine what is safe and what isn’t. ISPE’s Risk Mapp and EMA guidelines provide acceptable daily exposure to identify a safe amount and acceptable limit that you can administer by any route as an
acceptable carryover limit. A company can use them to establish cleaning limits for equipment that comes in contact with product.

Hazard assessment established for setting an OEL are based on inhalation by workers. Risk assessments for cleaning validation limits, however, are for patients taking the next drug and might include children or sensitive subgroups. You can’t take an OEL and multiply it by 10 to come up with a permitted daily exposure (PDE) or acceptable daily exposure (ADE). There is still some resistance to applying PDE and ADE to cleaning validation, but, in December this will be required in Europe.

We don’t look at this in great detail during a certification assessment, but we do look for health- and science-based limits.

This article originally appeared in Pharmaceutical Technology Outsourcing Resources Supplement, Vol. 39, No. 17, pp s18–s22 (August 2015).

Agnes Shanley is the senior editor of Pharmaceutical Technology.
Protecting workers, patients, and the environment requires advanced technologies.

The market for formulated drugs based on highly potent active pharmaceutical ingredients (HPAPIs) is growing at a rapid pace, largely due to the development of highly targeted therapies based on antibody-drug conjugates, which can include cytotoxic small-molecule components. The manufacture of this expanding field of HPAPIs is challenging and requires specific know-how, facilities, equipment, and procedures designed to mitigate the risk associated with producing and handling potent compounds. Standards and technologies are continually changing, and HPAPI manufacturers must remain vigilant and prepared to adopt and implement the latest designs, equipment, training, and procedures to reduce the risks posed by HPAPIs.

Dealing with uncertainty
Although many challenges exist for high-containment API manufacturing, the variability
and uncertainty associated with each compound present the greatest risks, according to Waldo Mossi, general manager of Helsinn Advanced Synthesis. “The importance of occupational exposure limits (OELs) is widely neglected in discovery research and early development,” he states. He explains that many companies use a one-size-fits-all approach to handling and managing the containment of bulk drug substances. Each individual process, however, offers different challenges, and no two new chemical entities (NCEs) are alike. The situation is aggravated by the lack of universally accepted definitions for various compound types, such as highly active, highly potent, and cytotoxic agents, which can lead to confusion between sponsor companies and custom-manufacturing organizations (CMOs), according to Mossi.

To manage the variation and address the uncertainty associated with new substances, Helsinn continues to strive for design of toxicology testing and safety evaluation from the early stages of process development. The company also uses a comprehensive, science-based OEL evaluation approach from the start of an HPAPI project, and works with experienced industrial hygienists to assign initially conservative OELs to each potent compound that will enter its facility. “Since a certain level of risk will always exist when working with HPAPIs, it is important to foster a strong company culture of excellence in protecting employees, products, and the environment. Our comprehensive approach to process and compound evaluation helps to clearly define the needs and objectives in handling each process step,” Mossi observes.

Fortunately, as an HPAPI project proceeds through the development lifecycle and into clinical trials, the understanding of the risks associated with the potent compound increases and risk mitigation generally becomes less difficult, according to Patrick Klipstine, director of SAFC’s Madison, WI site. “During the development process, SAFC pursues ongoing internal evaluations and works with third parties to bolster this process. As the definition of potency becomes better defined during the development cycle, our process engineers and environmental, health, and safety (EHS) representatives can make appropriate modifications to the manufacturing engineering controls,” he notes.

Manufacturing and process continuity are also crucial during scale up to ensure that risks are minimized, according to Mossi. “Laboratories and small-scale GMP equipment should be designed so that they are aligned with the large-scale equipment used for commercial
production in order to ease the transition and reduce uncertainty and risk during scale up,” he says. At Helsinn, the risk associated with scale up is reduced through facility design and investigated during early design of experiment (DOE) analyses.

More than chemistry
In any chemical manufacturing plant, the protection of operators is a top priority. In facilities producing HPAPIs, providing operator protection is absolutely critical and the top priority, according to Klipstine, which means that appropriate engineering controls are in place and personal protective equipment is available. In addition, every unit operation must be considered with regard to both the chemistry and potential occupational exposure.

“Chemical processing steps are evaluated on their merits with regard to sound chemical process hazard criteria, and then each process is developed to allow for the safest execution of the process within the identified equipment train, taking into consideration compatibility with materials of construction, thermal output, gas evolution, waste stream management, etc.,” Klipstine notes. With these considerations taken into account, SAFC then applies engineering controls for containment to mitigate the risk for occupational exposure. Specifically, the company has adopted a risk-minimization strategy that is systematically constant, but allows for different outcomes depending on the chemistry and potency of each API.

In addition to variable chemistry, operational risk depends greatly on several factors, including the company culture, personnel training, proper operational execution, and the design and engineering of the facility.

“Each opportunity that turns into a project goes through a defined risk assessment process, with experts in our process development, EHS, and process engineering groups closely collaborating to provide a robust process from both a chemical engineering and process engineering standpoint. One of SAFC’s first principles is that all processing of powders and liquids are conducted in closed systems that have been verified to be effective for the prevention of occupational exposure. Second tier to these systems are robust training programs that have been designed for specific unit operations,” he adds.

Helsinn also emphasizes the use of fully closed systems and isolation to
avoid or mitigate areas of greatest risk. The company fosters the approach of contained chemistry, which means that equipment for each individual process (e.g., balances, rotary dryers, pressure filter dryers, and slurry vessels) is installed inside an isolator that has been qualified for occupational exposure levels down to nanogram levels according to the International Society for Pharmaceutical Engineering’s (ISPE) Standardized Measurement of Equipment Particulate Airborne Concentration (SMEPAC) methodology. The use of such an approach, according to Mossi, was made possible by a clean atmosphere design supported by accurate general ventilation using double-pass, high-efficiency particulate arrestance (HEPA) filtration.

It should also be noted, according to Mossi, that in addition to variable chemistry, operational risk depends greatly on several factors, including the company culture, personnel training, proper operational execution, and the design and engineering of the facility. In general, the greatest challenges are typically associated with operations such as sampling, loading/unloading of the reactor, and transfer of the material. “Powder handling presents the highest probability for potential worker exposure, and it is important to carefully study optimal methods for minimizing and, wherever possible, removing powder handling operations from an HPAPI process,” he states. At Helsinn, if powder handling is necessary, effective and consistent safeguards are factored in with redundancies to mitigate the risk even further.

SAFC handles both liquid and powder HPAPIs under a defined set of unit operations to minimize the potential for occupational exposure. “By using one common system defined appropriately for scale to ensure containment, our chemists can be assured that the processes they are executing are appropriately identified for the defined potency,” Klipstine explains. To reduce risk, all large-scale isolation of powders is conducted in jacketed filter dryers where solids can be filtered and dried without the necessity for discharge from the drying unit operation. Once dry, the HPAPI is discharged using glove-box containment techniques directly into predefined drug-substance packaging using ILC Dover continuous liner technologies, according to Klipstine. As a best practice, Helsinn investigates each manufacturing process step for hazard and safety together with the aid of an outside industry expert as part of its DOE analysis.

**Cross-contamination prevention**
Of significance to HPAPI producers is having a thorough understanding of
the cleaning procedures required to meet allowable carryover limits for multipurpose equipment, according to Klipstine. “Controlling cross-over contamination mitigates any potential risk to patients,” he asserts. Mossi agrees that safety cleaning verification at each stage of a manufacturing process and GMP cleaning validation is crucial. SAFC’s philosophy is to apply a continuous improvement mentality so that its systems will exceed current industry standards. Even so, one challenge the company faces regularly as a CMO with a multipurpose facility relates to servicing customers ranging from virtual biotechnology firms to large pharmaceutical manufacturers that have a wide range of expectations regarding handling and cleaning verification.

**Constant evolution**

Another challenge for CMOs that offer HPAPI manufacturing services is the continual evolution of industry standards and technologies. “Companies that want to participate in this market must adopt these newer technologies,” Klipstine asserts. SAFC, for example, had to transition to more robust analytical technologies with improved sensitivity and detection levels that allow for the determination of potential API carryover at part-per-billion levels.

On the other hand, as the industry continues to mature, consultants and innovative equipment manufacturers can help design state-of-the-art engineering controls to better suit specific facility containment requirements, according to Mossi. He notes that Helsinn’s recent facility expansion was custom-designed to support workflow, ergonomics, and safety, while containing several unit operations within only a few isolators.


*Cynthia A. Challener, PhD,* is a contributing editor to *Pharmaceutical Technology.*
potent compounds. integrated solutions. reliably supplied.

POTENT HANDLING EXPERTISE
Proven track record with 20+ years of potent handling experience and 80+ years providing innovative pharmaceutical delivery solutions. 300+ potent and highly-potent compounds, as well as hormones and cytotoxics.

INTEGRATED SERVICES
Integrated analytical, development and supply solutions with recent investments in high potency clinical packaging, Micron Technologies particle size engineering, and expanded manufacturing services for oral solids.

SAFELY & RELIABLY SUPPLIED
Robust engineering and PPE controls. Comprehensive risk assessment processes. Highly-trained, experienced team with deep expertise in special handling protocols in 10+ sites across our global network.

10+ SITES IN THE GLOBAL NETWORK
Integrated solutions from optimization through supply

20+ YEARS EXPERTISE IN HIGH POTENT HANDLING
80+ years providing drug delivery solutions

300+ POTENT COMPOUNDS HANDLED
Potent, highly potent, hormones and cytotoxics
The author reviews some of the key considerations when selecting a vendor and crucial parameters that must be defined in the tech-transfer process to ensure the greatest chance of success.

For a company looking for an outsourcing partner for pharmaceutical manufacturing, the choice is vast: from companies offering solely contract manufacturing capabilities, to those with niche technologies to assist development, or even ones with specific experience in certain dosage forms. Choosing the right partner could be based on the individual project’s requirements, be it specialist handling requirements or a bespoke technology need; or it could be because the outsourcing partner has preferred status. Whatever the reasons, a successful transfer of technology is a vital element.

**Key considerations in outsourcing**
The decision on how and where a new product will be manufactured needs to be made before a company files for regulatory approval. The sooner
an outsourcing partner can be included into the product development team to evaluate the process and its future needs, the more time there is to prepare the partner’s own staff for the technology transfer process, and the more likely the chances of success.

Seeking a credible and suitable partner, however, stretches further than technological proficiency or available capacity. Logistical implications, for example, should be taken into account, because the change of site and scale may require seeking a new source of API or excipients as well as lead to difficulties once large-scale production is necessary. A formulation that has certain, specific properties at small scale, such as attracting an electric-static charge, could be undesirable and difficult to handle at large scale.

Sources of excipients, which are in many cases commodity materials, need to be found at larger scale, and these sources may be different than the suppliers used in development and initial scale-up phases. Validation of both suppliers and products needs to occur. Where processes are transferred overseas, security of supply and quality of product must be ensured.

**Tech transfer challenges**

Despite all efforts, it is inevitable that there will be subtle differences in equipment and techniques between partners during tech transfer. It is, therefore, crucial that all analytical methodologies are fully disclosed and validated to ensure that any difference in data can be fully investigated. All methods should be discussed openly between partners before the transfer takes place to minimize the chances of a problem occurring further along in the development process.

Stability issues with the final dosage form can arise; for this reason, the packaging of the product needs to be defined at the commercial manufacturing stage and be available for stability studies. Any issues identified in these stability studies that do not directly affect the tech transfer could still have significant consequences for the product development timetable. It is important to define as soon as possible the cause of stability failures to ensure that what may be thought to be an unstable formulation is not because of in-vitro in-vivo correlation (IVIVC) issues, or incompatibility between an API and excipient, or a result of processing issues during a batch manufacture.

**Equipment differences**

Perhaps the most overlooked cause of issues in technology transfer is differences in equipment, even ones that are seemingly minor. The major
pieces of processing equipment, such as reactors, tablet presses, dosage form fillers, and packaging machinery will be clearly defined, but it may not be the case for much of the other equipment that is required. For example, the pumping system, the spraying system, the mixer and mixing tank, and the fabricator may not be defined, even though they can have a significant impact on the ultimate output of the process. The specification and purchase of a whole range of equipment must also be considered, such as filter bags or cartridges, vibratory sifting screens and mill baskets, and even the tooling for the tablet press.

Once raw-material suppliers have been sourced, equipment lists prepared and planned, analytical testing requirements confirmed, and any additional partners such as contract testing laboratories for materials identified, standard operating procedures (SOPs) need to be drafted and agreed upon, followed by validation. Potential bottlenecks and long lead-time items will have to be identified, and necessary items must be ordered in good time to prevent delays that hold up production and have a negative impact on timelines. If equipment is not already available on site, it must be sourced and purchased. Everything must be installed, calibrated, and validated. SOPs for both operation and cleaning processes must be determined.

Assays for either in-process testing or lot-release must also be transferred and, if necessary, third-party labs must be identified and audited. Documentation requirements are also extensive, ranging from the generation of process flow diagrams to the development of SOPs across the board including all relevant quality considerations.

**Scheduling**

Budgets and expectations should be set to include mitigation for delays and potential issues during the technology transfer phase of the project. An understanding of how capital investments will be shared needs to be agreed upon and a consensus reached at the outset about how any additional charges that arise during the transfer activities will be addressed.

The transfer schedule should be locked in at least 90 days in advance. A similar schedule should be set for commercial manufacturing, with allowances built in for surge capacity. Launch plans need to include a view on capacity at the plant and whether a partner can offer a capacity reservation option. For maximum efficiency in a technology transfer, all parties should also have a vested interest in the long-term success of the project.

**Choosing the right partner**

The right contract development and manufacturing organization for any
project will be able to combine its expertise of highly specialized services, dedicated infrastructure, and focused personnel to efficiently provide clients with a quality product both on time and on budget. The effective technology transfer of any dosage form to a third-party manufacturer requires honesty, openness, effective team management, and communication between all the stakeholders. Technical expertise and efficient process transfer and engineering runs are crucial, but the most important factor will be the development of a good working relationship between all the parties involved, based on mutual trust and cooperation.


Michael Valazza is vice-president, Global Business Development, Catalent.