Containment of high-potency drug products: Outsourcing and other challenges

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Courtesy of Metrics, Greenville, NC

In this article, outsourcing providers, containment equipment providers, and consultants discuss containment challenges, including outsourcing, scale-up, and product and operator safety.

API potency is defined by its occupational exposure limit (OEL). At or below 10 micrograms per cubic meter, an API is generally considered potent. Below 1 microgram per cubic meter, an API is generally considered highly potent. Manufacturing that involves potent APIs poses many challenges, so companies either dedicate equipment to the task or outsource operations to a third party, typically a contract manufacturing organization (CMO). These CMOs have the equipment and expertise that many companies lack.

The primary reason for containment is to protect the operator from potentially harmful products, even when that potential is not understood. "In early-phase development, you just don't have a lot of tox information, so there are a lot of unknowns," said Joe Cascone, director of potent pharmaceutical development at Metrics, Greenville, NC. "We may have some animal tox data, but since we're working on first-in-man, IND-type development and clinical supply and manufacture, there is no human data out there. You have no idea what kind of impact this compound could have on the body." And in this case, relying on your eyes, nose, mouth, and skin is a bad idea. "With respect to knowing whether or not you are in an environment that is unsafe, your senses are of little use to you," said John Farris, chief executive officer, president, and certified industrial hygien-

Courtesy of ChargePoint Technology, Liverpool, UK

Operators use a split butterfly valve to ensure contained charging of a small-scale tablet press.

ist at SafeBridge Consultants, Mountain View, CA. "If a substance has poor warning properties, you will not be able to sense it at the level at which it first becomes hazardous." Many high-potency products are cytotoxic ones that, when dosed at low levels, may treat patients but harm workers who handle them during manufacturing. "A lot of the projects we work on are oncology-type products where the intent is to kill cells or interfere with cellular metabolism, so cytotoxic products are very dangerous," Cascone said. That's why extreme care must be taken to ensure operator safety. "We urge everyone to use what we call a precautionary principle," Farris said. "Assume that the drug is potent until it's proven that it isn't. That way, you'll never make a mistake and injure someone."

There are secondary reasons for containment, too. "You have the actual protection of the product itself—it could be very sensitive," said Ben Wylie, marketing executive at ChargePoint Technology, Liverpool, UK. "A further reason could be dust control, where there is no immediate risk to the operator, but you need to prevent dust from escaping into the operator environment for hygienic and cleanliness reasons. And obviously, if the equipment isn't controlling the dust or containing the product during processing, that means it's escaping somehow, so you're losing yield. By containing the process, you're maximizing yield."

Outsourcing a high-potency product

The numerous hurdles associated with containing high-potency APIs—from investing in equipment and training staff to operating specialized facilities—motivate many companies to outsource. "Obviously it's favorable for a lot of clients to outsource highly potent and cytotoxic compounds because either they prefer not to work with those materials in their facilities, or they don't have the capacity or the training to work with them," Cascone said. Also, CMOs often provide expertise that client companies may not have in house, according to Robin Mitchell, senior director of business development at PII, Hunt Valley, MD. "An outsource service company likely already has a lot of experience handling different containment products with procedures and setups in place. They're often better equipped to deal with the special handling requirements and the risk factors associated with those products." CMOs are also usually better equipped than client companies to invest in the necessary equipment or facility, according to Chris Calhoun, president of Norwich Pharmaceuticals, Norwich, NY. "It's much more efficient for a contract manufacturer like my company to make a single investment to benefit multiple customers and multiple products than it is for every single company that might have one or two high-potency products to make that same investment."

In addition, as drug products become more potent—many with OELs in the nanogram range—they're increasingly difficult to handle. "As we move up the spectrum of more potency and more toxicity in the drugs, it gets harder and harder to contain them," Farris said. That's one reason Cascone's company built a 3,000-square-foot GMP-compliant facility for processing high-potency products. "We definitely saw an uptick in both the frequency and the potency of the compounds that were coming our way," Cascone said. "When client companies asked if we could work with materials that had very low OELs, we had to turn them away. Thanks to the new facility, what we could permit on site dropped from 1 microgram to 30 nanograms per cubic meter of air in the breathing zone."

Minimizing or eliminating containment through the choice of dosage form is another strategy, according Mitchell. "Softgels, for example, are a solid dosage form that is particularly suited to containment formulation work. By putting the drug in liquid form at an early stage, you can avoid the downstream dust and powder handling issues associated with traditional tablet and hard capsule products, making it much safer and easier to handle."

But containing a high-potency drug product isn't as straightforward as simply delegating the project; you also must find the best CMO. "Do everything you normally would do to evaluate an outsourcing company," Mitchell said, "but pay more attention to understanding the specialized facilities, as well as the training and experience level of the people who are involved in that particular type of project, and also whether the company has well-designed risk management systems in place to assess what it's going to take to bring a containment product into their facility." And is the process up to snuff? To answer that question, a third-party company like Farris's (or the CMO itself) will conduct an assessment program to eval-

uate the containment and exposure control of the entire operation. The CMO receives certification if its facility and operation are deemed capable of handling potent drug products safely. The third party should also conduct performance verification to assess the efficacy of the containment equipment, typically by processing a nonpotent powder. "You manipulate a surrogate powder—it can be lactose, it can be mannitol—or a drug substance that's not potent, like naproxen sodium," Farris said. "The customer will specify, 'We want the containment equipment to achieve "X" as an air concentration.' We'll run the surrogate test using these powders, then send air monitoring samples to a lab, get them analyzed, and see if it met the limit." If the third party uses a surrogate powder to verify the containment, it should later rerun the test using the actual API. It should also have conducted a factory acceptance test and a site acceptance test (both of which typically include performance verification) to ensure that the containment equipment has been built and installed according to specifications.

Even though dealing with containment can be a big project, foregoing it to save time or money could actually cost much more down the road. "What's the business impact if something goes wrong and you overexpose people?" Farris said. "Well, first you shut production down because somebody got sick. Then you scare everybody else that didn't get sick. Now you've got a serious problem on your hands: Not only do you have to contain it, deal with the injured party, and deal with the concerned workers, but you have lost time. And time is money. How much does it cost if you're shut down? For a day, a week, a month, 6 months? That could calculate to $30 million if the drug development costs are $1 million a day and you're shut down for a month. All of a sudden, the $10,000 valve and the $70,000 isolator don't appear to be that expensive."

Containment challenges

No matter who—you or a CMO—handles the high-potency product, some challenges are bound to crop up. One challenge is containment at the R&D level. Paradoxically, R&D often requires higher containment than large-scale manufacturing, even though product quantities are smaller. "A lot of companies in R&D are handling multiple products, and they may not know the required containment levels of those products because they're still in the research phase," Wylie said. "Also, they may not know what products they're going to be handling next week—one week you could be processing Product A, which presents no risk, and the next week you could be processing Product B, which has a high OEL associated with it. Therefore, you need to cover all of the potential bases, so you should select equipment that is suitable for the highest product OELs you could be handling." It's best, according to Wylie, to choose versatile equipment for R&D if you're handling multiple products. "If you're going to be milling one week and tabletting the next week, you want containment solutions that cover all those eventualities. Also, a containment valve is highly versatile, because you can attach it to a wide variety of process equipment to safely transfer product to and from each of the production steps." Wylie's company offers a range of split butterfly valves capable of nanogram-level containment.

Indeed, materials transfer is another containment challenge. "Once you have a given blender or other piece of equipment charged with the product, it's generally easily contained. The hard part is moving the bulk powders down the equipment train," Cascone said. "The risks are increased while you're transporting bulk powders to and from the pieces of equipment." And such containment breaches do happen, no matter the level of containment. "From bench-scale chemistry, where you're making milligrams, all the way up to full commercial manufacture, there have been health effects with various drugs in various places. Some highly acute substances can cause respiratory arrest in 5 minutes, while some chronic ones might cause symptoms that don't develop for years," Farris said.

Scale-up can also be problematic. "Generally you can contain 1-kilogram batches with gloveboxes," said Cascone. "But you can't place commercial manufacturing pieces of equipment in a glovebox. The piece of equipment actually needs to be a pre-engineered, contained device. So you're talking about a good deal of capital to contain a commercial-scale process. Not only do you have to buy the equipment, you have to have it located in a room with stringent access controls, dedicated air handling, and negative differential pressure to protect against an accidental breach of containment."

Another challenge is deciding if and when to purchase equipment or to outsource the project. "You want to be in a position to start manufacturing your commercial product as soon as you get an approval from the FDA, but you don't want to spend all that money unless you know you're going to get an approval," said Cascone. "It's really difficult to time that capital expenditure right."

Retrofit versus buy new

There are a few different ways to achieve containment. One is to retrofit. "If you've already got a perfectly good tablet press, you don't want to buy another tablet press—you want to retrofit it and contain it," Cascone said. Many of Wylie's customers choose retrofitting to ready their facility for high-potency products. "We have customers that have approached us and said, 'We have all the equipment in place to process a particular product, but we've got a new product coming into the facility, and this product now has different health-safety requirements in terms of the OEL level,'" Wylie said. "And any change in regulation—health and safety or compliance—could also lead to retrofitting the existing equipment for high containment. It's just a case of bringing the design up to date for immediate or future eventualities in terms of production." But retrofitting isn't always a perfect solution. "It's a little bit cumbersome. You've got a piece now with a box around it rather than an integrated machine, and the person who designed it wasn't thinking about containing it," Cascone said.

The other way is to purchase new containment-ready equipment or to build a fully contained facility, as Cascone's company did. "We employed hard-wall isolation with stainless steel and glass barriers between the processes and the operators, instead of containing the operator in a suit with a respirator as is more customary. We've enclosed the process instead of the person," Cascone said. "The nice thing about buying new and customizing is we could specify a lot of things with the manufacturer to get exactly what we wanted." Farris sees a trend toward new equipment and facilities. "We're seeing more thought being given to controlling containment at the design phase rather than having to go back and retrofit old facilities. I'm encouraged that new fully contained facilities are becoming, in most cases, the dominant approach."

On the other hand, Norwich's Calhoun says a combination of retrofitting and buying new is the most realistic. "Handling high-potency compounds is a very expensive proposition, so unless you are working with a fixed set of compounds, you may spend significant resources installing equipment that is rarely used for its intended purpose. The trend we see is a mixture of two approaches: Start with flexible containment in your early work, where you're determining whether a product will be approved and manufactured, and save the capital equipment investments until you're confident that that investment is going to be put to good use." Last year, Calhoun's company built a pilot-scale facility that produces registration batches so companies can file their application with the FDA. "The facility allows us to operate at smaller scales to learn more about what's required for each product and how dust is generated. We then can be much more effective and efficient as we make the large-scale investments later. Pilot-scale development also allows our customers to make a small investment up front, instead of going into a large-scale production run and realizing some inefficiencies related to their compound," Calhoun said.

Product safety versus operator safety

Even with containment procedures in place, protecting the product and protecting the operator can be competing goals, Cascone said. "Right now you have two mutually exclusive regulatory landscapes. You've got the FDA, who is concerned with protecting the product, and you've got OSHA and environmental health and safety and industrial hygiene-type groups that are concerned with protecting the worker. There's no FDA requirement that you contain anything for the manufacture of solid dosage forms—the GMPs just don't address it. Historically, the processes and technologies customary to the manufacture of solid-orals weren't contained." Farris agreed. "Very few things that you do for GMP are designed to protect the worker. So historically the quality folks and the health and safety folks have been on opposite sides of the fence. Accomplishing both goals can be done, but one can't forget about the other. They have to keep the process under strict control, which means we're doing everything in our engineering control, process chemistry, and safety power to prevent the fire, explosion, or overexposure."

Cascone said his company's facility allows both goals to coexist. "When we opened up our facility, we went right away into GMP manufacture to support a Phase II clinical trial. Pretty much right off the bat, we did a campaign of six capsule batches in the new area. Not only did we successfully manufacture everything and release all of the batches to the clinic, the biggest pleasant surprise was that at the conclusion of the multi-batch manufacturing campaign, because all the containment was employed, we were left with an essentially clean room. So that demonstrates clearly that there are major GMP compliance benefits from containing your process."

Looking ahead

One trend on the horizon is more CMOs providing containment, Wylie said. "We have an increasing number of contractor and generic manufacturing customers. Also, we're seeing an increase in customers, particularly around China, India, Singapore, and South America. Some are relatively new to containment, so obviously they are developing at a fast pace to meet the required containment standards that a lot of the European and American markets already meet."

Another trend is an increase in facilities that are fully dedicated to containment. "There will be more facilities that are designed explicitly for containment and are operated separately from those for standard products," Mitchell of PII said. Cascone predicted a future with even more protection: "I wouldn't be surprised if, over time, we evolve toward absolutely everything being contained. Though right now, pretty much across the board, it is limited to products that are deemed highly potent or cytotoxic."

Calhoun and his colleagues are working to develop new strategies to minimize dust. "There are many more of these high-potency compounds in development compared to 10 years ago, and that increase is driving the innovation of new companies, new equipment, and new solutions. For instance, are there ways to lower dust generation in the first place? Can you wet the material, where it just simply doesn't create as much dust? Can you do things through particle size manipulation to create larger particles, so when the API is manufactured, it doesn't come to you in a dusty, difficult-to-control version? We're developing creative solutions to answer these customer needs from multiple angles."

For his part, Farris hopes for a more systematic approach to potent compound safety. "I'd like to see proper evaluation of the compounds, proper evaluation of the work environment through a combination of toxicology and industrial hygiene, building industrial hygiene databases around various activities so you know what can get you into trouble. It's more than just the hardware. You've got to have the evaluation pieces, the training pieces, the management commitment because you have to stay on top of it. At the end of the day, if you do it right, and you do it in a systematic and controlled fashion, no one will ever get sick in your plant. You'll never lose time for these issues and your plant will become more productive." *T&C*