



Aging Facilities: Aseptic Manufacturing Faces the Future

Agnes Shanley

Aging facilities and inadequate quality systems create drug shortages. Preventing them will require harmonized regulations, and management support for continuous improvement and innovation.

Over the past few years, severe and ongoing drug shortages have brought drug manufacturing plants, their operation and maintenance, into sharper focus. Aseptic processing and filling lines have been identified as a major source of problems, which can become critical when the sole supplier of a drug is also working in an outdated facility with old equipment and inadequate quality systems. According to FDA, 54% of injectable drug shortages have been due to quality problems, including particulate, microbial, or other contamination (1).

Some owners may run plants beyond their designed life expectancy, to recoup costs. The results will eventually show up, for example, in old water systems, or wall panels that breaks down and can become contaminated, explains Maik Jornitz, president of G-CON Manufacturing, and co-chair of the Parenteral Drug Association's (PDA) aging facilities task force, which is studying these issues.

One consultant who spoke about a major pharma consent decree at PDA's annual meeting in March 2015, explained that most pharma facilities are designed to run for 20 to 25 years. The four facilities cited in this decree, however, were all more than 30 years old. A few years after the company had invested more than \$500 million to improve infrastructure, water systems, IT, and environmental monitoring at the facilities and bring them into compliance, they were all shut down when the company was acquired.

New technologies including mobile cleanrooms and isolators, combined with single-use process technologies, promise a future of agile, flexible facilities (see **Sidebar**), if their adoption can be encouraged. This article explores some efforts that are now under

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way to study root causes of drug shortages and to facilitate dialogue between companies and regulatory agencies. The goal is to improve operations in existing facilities and to spur adoption of new technologies, both of which are key to ensuring stable pharmaceutical supplies in the future.

The first extensive research into the causes of drug shortages, an industry survey (2) by the International Society for Pharmaceutical Engineering (ISPE) in 2013, found that faulty facility maintenance and operations, and old infrastructure problems, were behind many pharmaceutical quality issues and shortages. Eighty percent of the survey's 264 respondents, for instance, linked

shortages to problems with sterile manufacturing equipment.

In 2014, PDA set up an expert working group to analyze how aging facilities contribute to drug shortages, breaking the topic down into three key, interconnected areas: facilities, processes, and analytics. "If you touch, or fail to improve, just one of these areas, all are affected," says board member Robert Dream, principal of HDR Co., who heads up the Process subgroup.

Dream, who has worked on aseptic manufacturing facilities using nontraditional technology, defines his subgroup's mission: to analyze available technologies and offer guidance on how to upgrade

Enabling tomorrow's flexible facilities

A number of technologies have been available for some time to help pharma improve the safety, sterility, and efficiency of its aseptic processes. Today, combined with single-use processing systems and new flexible construction platforms, these technologies permit drug manufacturing to become more responsive and targeted than it could be in the past.

Isolators, first called "gloveboxes" and used in the nuclear industry, were introduced in the 1980s as an alternative to cleanroom construction. They create an airtight enclosure around a process, or process equipment, protecting product from contamination, or operators and the environment from exposure to highly active materials. Gary Partington of Walker Barrier Systems discussed these and other alternatives at INTERPHEX 2015.

Restricted access barriers (RABs) have also opened up new possibilities, providing rigid enclosures around equipment. Mobile cleanrooms are also available, says Tom Wyss, director of sales at Walker, as well as "downflow booths," designed mainly for processing powders, which look like mobile cleanrooms but are mounted inside a facility, using the facility's floor. These booths require facility airlocks and process control, similar to mobile cleanroom.

Mobile cleanrooms are made from aluminum, and whole units are shipped on trailer. Each one is taken off cranes and inserted, then utilities are hooked up, including compressed air, process gases, and waste disposal trains, says Wyss. They can be taken

apart and reassembled, he says. Designs range from generic to highly customized.

The mobile cleanrooms are less expensive to build and operate than traditional cleanrooms, says Wyss. As his colleague, Gary Partington, showed at INTERPHEX 2015, installing a mobile cleanroom with HVAC, HEPA filtration, and sensors can shave considerable amounts from the costs and timelines required for traditional buildings.

Walker is an offshoot of Wabash National Corp., an Indiana-based firm that specializes in over-the-road transportation and semitrailers. Its pharma business started in the 1980s, and its mobile products are built from aluminum and designed to withstand the rigors of the road. The company has also been making mobile laboratories since 1997, through a sister company in the United Kingdom. "Conceptually, this idea is now taking hold in the industry. The European market showed interest earlier," says Wyss. Another company offering mobile cleanroom, containment, and isolator technology for pharmaceutical manufacturing is Germ-Free, based in Florida.

Offering a different approach to flexibility is G-CON Manufacturing, whose PODS are prefabricated, self-standing containment cleanroom systems. These units feature integrated air bearings, which make them easy to move. They can be connected to centralized chilled water and electricity, and interconnected via transfer ports, and decontaminated via standard treatment with vaporized hydrogen peroxide.

systems, support systems, or containment around a process without causing such major change that regulators consider the modification a new process.

It's a delicate balancing act. "When we started looking into aging facilities, we realized that we'd opened a big can of worms," says PDA Group co-chair Jornitz. "It's a hot topic that needs to be addressed on multiple levels, including continuous improvement, proper maintenance protocol, training, and regulatory post-approval protocol," he says.

One biopharm company professional said, during an FDA inspection, 'Please write this up and put it in a 483. That's the only way that we can get upper management to pay attention to this type of thing.'

To promote greater awareness and discussion, PDA created an open forum on aging facilities for industry professionals to exchange experiences and opinions. A three-day track of sessions was devoted to the topic at INTERPHEX 2015. PDA has invited regulatory agencies to take part in the discussion and encouraged companies to communicate issues to regulators.

At a time when more technologies are available than ever before to improve aseptic operations and product quality, companies are reluctant to invest in and install them. One reason, Jornitz says, is that some senior managers may not fully understand the costs of poor quality and supply problems and how new technology could save money in the long-term.

However, regulatory questions pose an even deeper challenge. Companies are often reluctant to invest in and install technologies that would

benefit them, out of fear that regulators will view their use as a major process change, triggering re-testing and delays.

PDA will soon launch an industry survey to focus more closely on such issues as continuous improvement, maintenance, and a unified change system that can be adopted globally, Jornitz says. "Right now, it can take four years to run through a post-approval change (PAC), which is a crazy burden on the industry," he adds.

Lack of harmonization in global regulations is another hurdle, adding complexity to day-to-day operations, Jornitz says. "If they make a change and then have to run three or four slightly different pro-

cesses in parallel, just to satisfy some regulator somewhere in the world, it's easy to understand why many companies won't adopt new technology," he says. "Ultimately, the human factor can come into play and cause problems," he says.

A good example of what can go wrong is Ben Venue Labs, a contract manufacturing organization (CMO) in Ohio that experienced major problems running its sterile operations. The company was issued a Consent Decree, and then went out of business. As Dream explains, at one point, the company had 163 products for 20 clients in 40 countries. "Think about trying to modify or improve a process under those conditions. You're up a tree," he says. And it's not an unusual situation for pharma companies today.

Harmonization efforts have progressed since FDA joined the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-ope-

tion Scheme (PIC/S), which includes 46 regulatory agencies from all over the world, says Dream. “On newer facilities, we have a leeway that we didn’t in the past. For instance, we can get certification from PIC/S, rather than just FDA or the European Medicines Agency (EMA), so if you change anything, you can make the change based on PIC/S. It simplifies things.”

Standardizing post-approval changes

PACs remain a serious challenge, however. At PDA’s 2015 annual meeting, former chairman Anders Vinther discussed how they might be standardized, to prevent shortages and industry’s overreliance on older technology and the status quo. He said that companies are prevented from modernizing and implementing continuous improvement by reporting, documentation, and approval processes that can vary greatly, not only from country to country, but even from person to person in the same regulatory agency.

FDA staffers clearly have a heavy workload. At INTERPHEX 2015, Laurie Norwood, deputy director for FDA’s division of manufacturing and product quality, center for biologic evaluation and research (CBER), noted that, at any time, each of CBER’s 30 reviewers can have 23 biologic license applications (BLAs) and 10 other supplements to review, plus Type A,B,C meetings with industry to coordinate.

However, despite the resource crunch, duplicate reviews and inspections still occur, Vinther said, and current PAC processes only encourage industry to maintain the status quo. He suggests that industry advocate for the development of a single global comparability protocol, and proposes the following:

- one set of reporting levels (critical, serious, not serious), defined globally
- the same reporting level and same approval time line for same change, regardless of country
- one country PAC lead for each product, around the world.

Communication with regulators is important, noted FDA’s Norwood at INTERPHEX. As she explained, even in the International Council for Harmonization’s (ICH) Q8 guidance for pharmaceutical development, there was always an expectation that facilities be properly maintained. ICH’s Q10 guidance on quality systems identified actions for improvement, and the need for management to support continuous improvement, while FDA’s newer process validation guidance requires a state of control, throughout the lifecycle of any process. “The process cannot be in control if your facilities are not,” she said. Norwood, and experts on PDA’s taskforce, agree that management support is essential to improving quality systems as well as plant operations and maintenance. There is a need to be lean in operating the facility, Jornitz says, but to ensure continuous improvement.

“If you want to run a process down to the ground to get as much money out of it as you can, you may eventually get a consent decree. The fines cost a lot more than facility improvements,” says Dream. At INTERPHEX, Norwood informally recalled what one biopharm professional said during an FDA inspection, ‘Please write this up and put it in a 483. That’s the only way that we can get upper management to pay attention to this type of thing’. Norwood called for proactive risk assessment and a systematic approach to recapitalization. “Build for the future, but, if you acquire an older facility,

do a thorough risk assessment and recapitalization project, and reinvest in it for the future,” she said, noting that, all too often, this is done after failure. “This should be part of quality systems,” she said.

At PDA’s 2015 meeting, Jason Duff, director of profiling and design oversight at Lilly Engineering, shared best practices from his company. He described a recapitalization assessment program that Lilly started in the early 2000s to remove subjectivity from asset evaluation, and establish the engineering department as owner of the process.

Addressing both operationally obsolete equipment and systems (which cannot be repaired) and functionally obsolete systems, the company identifies asset investment projects on two- and five-year timeframes. Individual sites analyze data, including asset performance, capability, and historical maintenance data. The central engineering group then reviews these data to develop plans and timelines, and estimates asset replacement value.

Tales from the aging facilities front

Norwood also emphasized the importance of basic infrastructure, particularly HVAC and water systems, and preventing biofilm and bioburden formation. She then recounted examples of aging facility issues she had seen at biopharma companies. In one case, a company moved from an open to a closed system, replacing roller bottle technology for vaccine development, to beads within the fermenter, fed via ports, using disposable process equipment and quick connects to minimize potential for cross-contamination.

“This project needed a lot of R&D work because, initially, the move to beads lowered the product yield, and they needed to change medium. However, the work ultimately reduced risk and also

prevented product loss,” Norwood said.

In another case, a company’s virus inactivation testing system failed. Old-time employees know what to do in this type of situation, but, when they retired or left the company, their knowledge was not transferred to new recruits. As a result, a new employee moved the filter integrity tester to the wrong side of the facility during an inspection.

Early communication is essential

Norwood recalled an example of how vital communication can be in recounting what happened at one old sole-source vaccine plant. FDA had noted its tendency to be out of control, and the company was planning a new facility. It made an interim plan for the existing plant, and FDA allowed it to submit a Changes Being Effected (CBE or CBE-30), so that it could keep product going with only a small amount of inventory. The supplement is required for any change to a product that could have some adverse impact on identity, strength, quality, purity or potency. Product made with equipment incorporating the change may be distributed within 30 days.

The company had one filling line and made five or six vaccines, Norwood said. Its managers had proposed changing from conventional filling to a restricted access barrier system (RABS). The company had requested a Type C meeting with FDA. It submitted its PAC supplement, but then an inspector visited the facility without prior warning.

It turned out that the company had changed its CMO for drug substance and had not communicated the change to FDA. This lack of communication led to delays in approval. In addition, inspectors found process and equipment failures, weak tech transfer protocols, and quality systems. Staff

could not locate five or six batch records. As a result, the company was issued a 483, and it took years for its quality systems to become sufficiently robust, Norwood said.

Norwood says that FDA's Center for Drug Evaluation and Research (CDER) allows companies to add a change to a RABS system and barrier under the annual report, as a way of protecting product from the human element. In addition, she said, more companies are using the CB-30 comparability protocol, which does not require facility shutdown. "The tools are there, but you need to use them," she said. "Don't be afraid of us."

Single-use implications

Single-use equipment, which eliminates the need for cleaning validation, is becoming extremely popular in biopharma operations. However, Jornitz sees a need for caution. Companies must take into account the design and layout changes that single-use equipment requires. "Too many people simply layer single-use onto a flawed foundation," he says. "You cannot just shove it into an aging infrastructure where you don't have the right possibilities for moving material and personnel," he says.

The future promises nimble, flexible facilities. For biopharma, Texas A&M has been an incubator for innovation, with facilities such as Caliber Biotherapeutics' plant-based biopharm manufacturing site in Bryan, Texas, or the Center for Innovation in Biopharmaceutical Manufacturing. Using portable, self-contained GMP modules, and mobile cleanrooms, as well as single-use equipment, the facilities embody new goals to reduce the time required to introduce vaccines from years to months.

Another glimpse of the future can be seen in the Portable, Continuous, Miniature and Modu-

lar (PCMM) platform, developed by G-CON, GEA Pharma Systems, and Pfizer. The system uses continuous processing equipment, smart control systems, and portable modules to process API powders and inactive ingredients into bulk tablets, and won an award at INTERPHEX 2015.

No more pharma palaces

"In the future, the industry won't be creating the old glass houses, or pharma palaces anymore," says Jornitz. "We need to become lean and mean and flexible. We need to build shell buildings (e.g., warehouse buildings) and install prefabricated modular cleanrooms into these buildings."

Dream sees these projects ushering in smart inventory management and the death of the warehouse, because raw materials could be brought in, and finished products removed, by the same truck. "Such buildings will shrink footprints and end up being more sustainable, requiring less land and less energy than traditional pharmaceutical manufacturing facilities," he says.

Facilities like this, and continuous manufacturing, are still far from the norm. Industry efforts, however, aim to destroy the roadblocks in aseptic processing and drug manufacturing that can lead to drug shortages. By discovering, and addressing, the roots of these problems, and opening up communication, programs led by PDA and ISPE can only benefit the patients who depend on the industry's products.

References

1. R. Friedman, CDER Update, University of Georgia GMP Conference, 2011, www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM252033.pdf
2. ISPE, *Report on the ISPE Drug Shortages Survey*, 2013, www.ispe.org/drug-shortages-initiative/about-the-survey **PT**