

## CMOs in the forefront of contamination control

*Pharmaceutical outsourcing taps the expertise and flexibility of contract manufacturing organizations*

**By Sarah Fister Gale**

Small and large pharmaceutical companies are beginning to see the value in exporting highly technical manufacturing processes (like production and packaging of products) to contract manufacturing organizations (CMOs). These third-party specialists have the expertise and facilities to meet the changing scale of production needs while improving contamination control strategies and meeting ever more stringent guidance from the U.S. Food and Drug Administration (FDA; [www.fda.gov](http://www.fda.gov)).



In fact, according to a Kalorama Information (New York; [www.KaloramaInformation.com](http://www.KaloramaInformation.com)) Market Intelligence Report, called "Pharmaceutical Outsourcing Opportunities Post Launch," the U.S. market for outsourced pharmaceutical manufacturing is growing at the rate of 10 to 12 percent annually. Pharmaceutical and biotechnology companies will continue to outsource an increasing number of products and services as a way to cut costs and focus on core competencies, says Steve Heffner, president of Kalorama and co-author of the report. "Manufacturing biologics requires a cGMP environment, specialized equipment, and experienced personnel with a complex set of skills to manage and run these facilities," Heffner notes. "Speed-to-market has become a major factor in the move to outsourcing. As generic drugs and alternative therapies pose strong challenges, there is increased pressure for pharmaceutical companies to get as much value as possible out of their patents."

### **Quality control and CMOs**

For CMOs, the trend toward outsourcing means lucrative business flows their way, but it also burdens them with much of the risk and challenge associated with contamination control. Every new client a CMO brings to the table comes with a lot of paperwork and protocol adherence expectations, notes David

Hussong, associate director for new drug microbiology in the office of Pharmaceutical Science at the FDA. "A CMO could be making hundreds of products from different companies, which means a lot more paperwork and a lot of audits."

Nowhere is quality and the control of contamination more of an issue than in pharmaceutical manufacturing. The smallest error in an aseptic processing environment could result in the manifestation of bacteria or other contaminants putting already vulnerable lives in danger. Beyond the health risks, a single contamination incident can have enormous financial and social implications for pharmaceutical manufacturers. As a result, anyone involved in the manufacture of pharmaceuticals must adhere to stringent cleaning and sanitation protocols and a zero tolerance policy for error at all times.

CMOs face even greater challenges than in-house production facilities, because not only do they need to address internal GMP processes, they also must meet and validate the expectations of clients, third-party auditors and, most importantly, the FDA. "Keeping all of those files updated can be worse than doing your taxes," Hussong quips.

Most CMOs agree that, while the risk is high and the complexities of managing multiple products is challenging, they have the systems in place to better handle contamination control risks in a more financially prudent format than in-house manufacturing facilities. "With exposure to so many diverse products and processes, a contract facility is typically designed with more versatility than you might find for a dedicated manufacturing line in a Big Pharma, which is pumping out a significant annual volume of the same commercial product," says Trent Cox, a microbiologist for Baxter International, a global diversified healthcare company and CMO based in Deerfield, IL ([www.baxter.com](http://www.baxter.com)). "As a multi-product contract manufacturing facility, there is a continuous focus on removing the risk of product cross-contamination."

Big Pharma companies have the tendency to develop their own philosophies and interpretations of regulatory guidelines, which in some cases can become part of the organizational culture for many years and difficult to change, Cox says. CMOs on the other hand, require more flexibility. Because CMOs must conform to the needs of each client, they are often faced with the challenge of finding a universal approach that will meet not only the regulatory guidelines, but also be accepted by each of the quality auditors from the many different client organizations. "This gives contract facilities excellent visibility to many alternatives, including new technology, and also forces a robust program to withstand numerous client and regulatory audits."

This flexibility and understanding of multiple techniques and technologies gives CMOs a competitive edge, and that edge may increase as the industry incorporates the recently released guidance from the FDA on aseptic processes for cleanrooms (see sidebar, "Updated guidance emphasizes training" on page 18).

### **Many CMOs already on board**

While the industry is anxious to get the new guidance, many CMOs long ago recognized the risks associated with personnel in an aseptic environment and

implemented stringent training and monitoring policies to secure their aseptic environments and to meet the expectations of clients.

"As a manufacturer of parenteral solutions and lyophilized products, there is a critical focus on microbial and pyrogen contamination control," Cox says.

"These topics are at the top of the list during all stages of project design and planning discussions."

From purchasing new, dedicated equipment for every product, to running non-stop training programs for new and existing employees, the priority for process design is minimizing risk. "Every part of our process is driven by established standard operating procedures [SOPs]. All our operators are trained on SOPs and have had hands-on experience in preparation and formulation procedures before they ever enter the aseptic environment," says Cox.

Baxter International has been in continuous growth mode for the last seven years, and in any given week, the company is likely to have three or four new hires going through its cleanroom operator training and qualification program. Many of the operators who are selected for training are internal candidates who've already been with the company for some time and seen what it takes to work in an aseptic cleanroom environment. For those new to the company, Baxter recruiters describe the job in detail and ask them to watch cleanroom operators in action to be sure this is a job they are interested in. "We have to look hard at the people we hire," Cox says. Even so, it's not uncommon for a trainee to opt out halfway through training.

The exhaustive six-week course begins with textbook training in a classroom where operators learn about aseptic procedures and technologies used in the cleanroom. They also learn the basics of microbiology, including common sources of contamination and the impact it can have. They complete written assessments at each phase of the training to ensure they've learned the material before moving on.

After the classroom, operators complete gowning qualification, which Cox considers one of the most important aspects of the new hire orientation. After watching gowning techniques performed, operators are expected to demo the gowning techniques while being observed by a qualified operator. The operator is rated and the gown is tested for contamination.

In the third phase of training, operators work in the cleanroom under the direct observation of a supervisor. At that time they perform a complete simulated media fill, which includes equipment set-up, receiving the media, sterile filtration set up and performance, and filling of sterile vials over the course of a predetermined amount of time.

As the final exam, operators perform a complete process media fill, which involves a full batch simulation on a filling line over 24 to 48 hours. "Even though it's a demo, everything is done using aseptic processes," Cox says. It's a much larger and longer process than the personal fill but he says by this point in the training operators are "pretty confident and they are familiar with all the equipment and parts."

Throughout the training course, trainees also work in the prep area, learning preparation processes, becoming familiar with assembly, wrapping and unwrapping procedures, and operating the autoclave. "It helps them to see what efforts are made with products and equipment prior to putting it in the cleanroom, and it gives them an opportunity to watch cleanroom operators through the viewing window before they are actually on the job," Cox says.

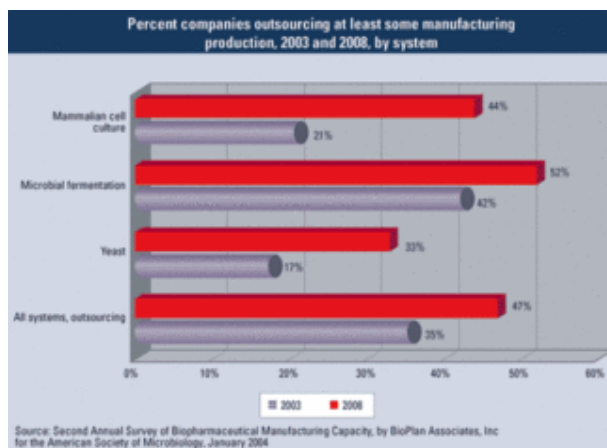
Along with new hire training, Baxter regularly offers employees cross training opportunities so they can be prepared for surges in demand and new product launches. "The basic principles of each product line are the same, so the training focuses on specific aseptic techniques and unique characteristics of individual products."

In biotech product development the need is even greater. "Facilities manufacturing biotech-based pharmaceuticals have had to step it up a notch when it comes to the processing environment," Cox notes. "Formulation steps once common in Class 100,000 cleanroom areas are now standard in Class 10,000 and Class 100 areas. It takes a well-designed process, skilled operators, and the right equipment made with the right materials to consistently perform this type of operation and maintain a high quality environment."

Cox believes biotech products have been a key driver in the use of restricted access barriers, isolators and automation, which are common efforts toward minimizing operator interaction during the aseptic process. "With cell-derived products, it is essential to maintain a pure culture during fermentation and downstream processing. Additionally, the nature of these compounds and the complexity of many biotech formulations restrict the use of terminal sterilization technologies for additional sterility assurance, which amplifies the importance of contamination control throughout the process."

### **Techniques to prevent cross contamination**

Along with training, CMOs invest a lot of design strategy and planning into eliminating cross contamination risks. CMOs face increased risk of cross contamination due to the large number of varied products produced simultaneously in a single facility. Sue Crow, director of quality assurance and validation at Lonza Biologics (Portsmouth, NH; [www.lonzabiologics.com](http://www.lonzabiologics.com)), a contract manufacturer of monoclonal antibodies and recombinant proteins derived from mammalian cell culture, says that in her facilities cross contamination from other products is prevented through campaign manufacturing, product changeover, and product-dedicated equipment and processing materials.



[Click here to enlarge image](#)

"Products are campaigned through the facility such that only one product may be in a process system at any time." Any reusable equipment, such as spinners, is dedicated to a cell line and is appropriately labeled. Between lots of the same product, the line equipment is cleaned and steamed if appropriate, using validated procedures. Between different products, a changeover procedure is performed that includes cleaning of equipment, elastomer change out and removal of product-dedicated processing materials. "Cleaning validation is performed on all process equipment to ensure that all elements of any previous process step are completely removed prior to the next process step," she says. "This is particularly relevant to vessels used for multiple steps in the same process, such as media and buffer preparation vessels." Lonza also uses disposable equipment and technologies where possible.

### The future is plastic

Dedicated equipment is one of the key components of contamination control for any pharmaceutical manufacturing environment—and also one of the most costly, notes Cox. For every new project, each piece of equipment and associated parts are purchased and committed to the life of that project. "They cannot ever be used on anything else, even a new product for the same client."

That means equipment purchases represent enormous capitol investment for every product and create a lot of leftover unusable goods when lines are changed or moved, notes Neil Holman, global marketing manager for Millipore ([www.millipore.com](http://www.millipore.com)), a pharmaceutical and biotechnologies products manufacturer based in Billerica, Mass. In an effort to lower equipment costs and further reduce risk of contamination, many manufacturers are opting for disposable alternatives to traditional equipment. Single-use technology is becoming increasingly common in pharmaceutical industry as manufacturers move toward incorporating disposables as a larger part of the aseptic manufacturing scheme. "Disposable is the hottest trend in pharmaceuticals because it offers so many benefits," Holman says. "It costs less, it's scalable and it reduces risk."

Global CSO market 2000-2010		
Year	CSO market (in millions)	Annual increase
2000	1,962	
2001	2,126	8%
2002	1,440	-32%
2003	1,643	14%
2004	1,889	15%
2005	2,192	16%
2006	2,542	16%
2007	2,924	15%
2008	3,362	15%
2009	3,900	16%
2010	4,524	16%
Compound annual growth rate		
2000-2005		2%
2000-2010		9%

Source: Kalorama Information, Inc.

Companies such as Millipore, Sartorius (United Kingdom; [www.sartorius.com](http://www.sartorius.com)) and Pall BioPharmaceuticals (East Hills, N.Y.; [www.pall.com](http://www.pall.com)) produce a range of disposable products, from filters to fittings to tubing and tank liners, that meet the needs of pharmaceutical manufacturers seeking lower-cost, more efficient alternatives to stainless steel.

With disposable sterile products, manufacturers don't have to invest as much up-front capital to launch a new pharmaceutical product line, Holman says. "They buy on an as-needed basis, and if the product goes away they aren't left with piles of unusable equipment."

Disposables also eliminate the need to clean, sterilize and validate equipment after each use. When the production process is completed, the disposable products are incinerated, which uses far less energy than it takes to clean and sterilize a comparable product.

As the various disposable technologies continue to improve, their use in biopharmaceutical and pharmaceutical processing will continue to expand. These devices provide reliable alternatives to cleaning validations, cutting costs and controlling contamination. "In the future, the pharmaceutical manufacturing process will be mostly plastic," Holman predicts, "and CMOs will be the first to make the transition. They are the early adopters."

---

## Updated guidance emphasizes training

On September 29, the FDA released the long-awaited update to the Industry

Guidance for Sterile Drug Products Produced by Aseptic Processing. The original document, authored and released in the 1980s, was a groundbreaking set of standards in an industry searching for direction on how to manage and maintain aseptic environments free of contamination risks, says David Hussong, associate director for new drug microbiology in the office of Pharmaceutical Science at the FDA. "At that time no other regulation document existed for aseptic environments, and it was a model for the others that came after it."

However, by the mid 1990s, it was clear the document needed to be revised. The original was based on an understanding of pharmaceutical processing developed in the 1970s and 1980s, says Rick Friedman, team leader of guidance and policy in the office of compliance at the FDA. "In the ensuing decades there were a lot of advancements in standards and technology and our understanding of aseptic processes evolved."

He also admits that there were informational gaps in some areas of the original—specifically in training and guidance for personnel—that needed to be filled. "The old document was sparing in its discussion of critical control points for personnel," he admits, and the team that authored the new document agreed it was a shortcoming that needed remedying. "Personnel can significantly affect the quality of the environment in which the sterile product is processed," Friedman says, noting that 80 percent of contamination incidences in an aseptic pharmaceutical environment can be attributed to personnel. Yet the original document paid little attention to the details of how to select and prepare cleanroom operators to minimize contamination risks.

Friedman's team dedicated an entire section of the new guidance specifically to training and the aseptic techniques that should be observed at all times in order to protect exposed sterile products from contamination.

"Unlike any other piece of equipment in a cleanroom, personnel carry millions of opportunistic microorganisms that pose serious risks to the aseptic products, especially those in injection dosages, which is why training is so critical," he says. "If certain microorganisms, such as E.coli, got into a product that was injected into a patient whose immune system is already weakened, it can be deadly." Injection doses are at the top of the hierarchy of risk and require the most scrutiny. However, any pharmaceutical produced in an aseptic environment demands the strictest adherence to sanitary procedures.

The new guidance for personnel encourages thorough training for all cleanroom personnel on the fundamental performance, including aseptic technique, cleanroom behavior, microbiology, hygiene, gowning, patient safety hazards posed by a non-sterile drug product, and the specific written procedures covering aseptic manufacturing area operations.

After initial training, the guidance suggests that cleanroom personnel and those performing aseptic sampling and microbiological laboratory analyses participate regularly in an ongoing training program as well as regular evaluations and vigilant monitoring. It states that: "Supervisory personnel should routinely evaluate each operator's conformance to written procedures during actual operations. Similarly, the quality control unit should provide

regular oversight of adherence to established, written procedures and aseptic technique during manufacturing operations."

According to the guidance, monitoring should be accomplished by obtaining surface samples of each operator's gloves on a daily basis, or in association with each lot. This sampling should be accompanied by an appropriate sampling frequency for other strategically selected locations of the gown. The quality control unit should establish a more comprehensive monitoring program for operators involved in operations that are especially labor intensive (for example, those requiring repeated or complex aseptic manipulations).

"An ongoing goal for manufacturing personnel in the aseptic processing room is to maintain contamination-free gloves and gowns throughout operations," Friedman says. "If operators exceed established levels of contamination or show an adverse trend, an investigation should be conducted." Follow-up actions may include increased sampling, increased observation, retraining, gowning requalification, and in certain instances, reassignment of the individual to operations outside of the aseptic manufacturing area.

---

## **Advice for cleanroom personnel**

*An excerpt from the FDA Guidance for Sterile Drug Products Produced by Aseptic Processing. The full guidance can be viewed at [www.fda.gov/cder/guidance/5882fnl.htm](http://www.fda.gov/cder/guidance/5882fnl.htm).*

Recognizing a gap in the original guidance for aseptic processing, the FDA dedicated a significant amount of space and thought to training techniques for personnel working in aseptic environments. Below is an excerpt from the guidance on appropriate behavior in an aseptic cleanroom.

**Contact sterile materials only with sterile instruments:** Sterile instruments should always be used in the handling of sterilized materials. Between uses, sterile instruments should be held under Class 100 (ISO 5) conditions and maintained in a manner that prevents contamination (such as, placed in sterilized containers). Instruments should be replaced as necessary throughout an operation.

After initial gowning, sterile gloves should be regularly sanitized or changed, as appropriate, to minimize the risk of contamination. Personnel should not directly contact sterile products, containers, closures, or critical surfaces with any part of their gown or gloves.

**Move slowly and deliberately:** Rapid movements can create unacceptable turbulence in a critical area. Such movements disrupt the unidirectional airflow, presenting a challenge beyond intended cleanroom design and control parameters. The principle of slow, careful movement should be followed throughout the cleanroom.

Keep the entire body out of the path of unidirectional airflow: Unidirectional airflow design is used to protect sterile equipment surfaces, container-



closures, and product. Disruption of the path of unidirectional flow air in the critical area can pose a risk to product sterility.

Approach a necessary manipulation in a manner that does not compromise sterility of the product. To maintain sterility of nearby sterile materials, a proper aseptic manipulation should be approached from the side and not above the product (in vertical unidirectional flow operations). Also, operators should refrain from speaking when in direct proximity to the critical area.

**Maintain proper gown control:** Prior to and throughout aseptic operations, an operator should not engage in any activity that poses an unreasonable contamination risk to the gown. Only personnel who are qualified and appropriately gowned should be permitted access to the aseptic manufacturing area. The gown should provide a barrier between the body and exposed sterilized materials and prevent contamination from particles generated by, and microorganisms shed from, the body. The Agency recommends gowns that are sterilized and nonshedding, and cover the skin and hair (face-masks, hoods, beard/moustache covers, protective goggles, and elastic gloves are examples of common elements of gowns). Written procedures should detail the methods used to don each gown component in an aseptic manner. An adequate barrier should be created by the overlapping of gown components (e.g., gloves overlapping sleeves). If an element of a gown is found to be torn or defective, it should be changed immediately. Gloves should be sanitized frequently.

There should be an established program to regularly assess or audit conformance of personnel to relevant aseptic manufacturing requirements. An aseptic gowning qualification program should assess the ability of a cleanroom operator to maintain the quality of the gown after performance of gowning procedures. We recommend that this assessment include microbiological surface sampling of several locations on a gown (e.g., glove fingers, facemask, forearm, chest). Sampling sites should be justified. Following an initial assessment of gowning, periodic requalification will provide for the monitoring of various gowning locations over a suitable period to ensure consistent acceptability of aseptic gowning techniques. Annual requalification is normally sufficient for those automated operations where personnel involvement is minimized and monitoring data indicate environmental control. For any aseptic processing operation, if adverse conditions occur, additional or more frequent requalification could be indicated.

To protect exposed sterilized product, personnel should maintain gown quality and strictly adhere to appropriate aseptic techniques. Written procedures should adequately address circumstances under which personnel should be retrained, requalified, or reassigned to other areas.

*CleanRooms* November, 2004

**Author(s)** : Sarah Fister Gale