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## Make Way for the Modular Cleanroom

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**Companies adopt quicker-to-build facility and cleanroom designs**



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Competition and pressure to keep prices down are factors pushing biopharmaceutical companies to get new products to market faster. This increased pace means they must design and build new facilities and cleanrooms faster while keeping contamination control a priority. The semiconductor industry faced similar pressures and responded by building more highly automated cleanrooms run by fewer humans.

"Pharma is viewing new facilities like semiconductor companies did 15 years ago," said Sterling Kline, director of project development at Integrated Project Services (IPS), a technical consulting and design company. It takes pharma companies three years to break ground, finish construction, and turn over the plant for qualification and validation. It takes semiconductor companies 12 months. "The pressures of Wall Street, pharmaceutical products coming off patents, healthcare costs, and return on R&D are changing the way pharma does projects. Pharma is now trying to build facilities that suit the product they think will be their next blockbuster."

But pharma faces different challenges than do semiconductor companies when bringing in new technologies. The process from fermentation to formulation is not the same as the electronics industry and generally involves more people, said Thomas Hansz, president of the consultancy Facility Planning and Resources Inc. (FPR). "The process is semi-automated in pharma," he said. "There are always people transferring things along."

In addition, biopharma companies are generally slower to adopt new technologies. However, they are opening up to two new ideas: isolators, which are essentially closed glass hoods that surround manufacturing equipment and are accessible to humans through glove ports, and modular walls and ceilings that are prefabricated off-site. Both technologies are gaining traction after having ramped up for the past several years. And both minimize the impact of humans, who remain the biggest contamination risk by shedding hair and skin and breathing moisture into the air.

"The [biopharma] industry is a technology-driven business that is conservative at the same time. It makes improvements on what has worked before rather than wholesale changes. So it is evolutions, not revolutions," said

Bryan Phelan, managing partner at AdvanceTEC LLC, a contractor that designs and builds cleanrooms. And while pharma has resisted an influx of ideas from the semiconductor industry to some extent, it is starting to open up to cross-pollination. "People who built semiconductor plants 10 to 15 years ago now have careers with pharma plants," Phelan said. There are areas that do not translate, however, such as airflow requirements and finishes on cleanroom surfaces.

Still, the industries are more alike than either wants to admit, said Tim Loughran, a consultant currently working with Cleanroom Construction Associates LLC, formerly with AdvanceTEC. "We did a project for Cambrex Biosciences where we applied microelectronics technology to a biotech research facility by using utility chases [a corridor behind the wall] that biotech and pharma hadn't considered."

Added Ralph Kraft, president of cleanroom services company R. Kraft Inc., "People need to look at their process from outside the box and ask, 'What can I use from semiconductors in pharma?'"

## Going Modular



A walkable, modular ceiling above the cleanroom allows equipment, ductwork, and utilities to be installed in the overhead crawl space at the same time the cleanroom below is being built. Sequencing the construction process can trim weeks to months off factory construction time.

Cambrex and Merck are among the growing number of companies installing prefabricated, modular walls and ceilings instead of traditional studs and dry wall construction. One big difference is that the modules are cleaner than dry wall, which puts particulates into the air when it is cut to size during construction or if a cart hits it in an operational plant. Manufacturers such as Plascore and AES Clean Technology build the modules offsite; they are then assembled at the manufacturing site, either a new plant or a retrofit.

Plascore's wall panels are up to 4 feet wide and 12 feet long, and they are made with an aluminum honeycomb internal structure and a coating of antimicrobial unplasticized polyvinyl chloride or uPVC, which is said to hold up better than painted walls and is chemically resistant to cleaners. They also have coved (rounded) corners, chemically cold-welded seams, and as few ledges as possible to reduce particle trapping. "There is a general trend away from dry wall toward metal composite," said Matt DeFer, product development engineer at Plascore. "It is a very nonporous finish."

Decreasing latent particles can make a huge difference. "Modular systems create a much cleaner work site. If you do have to cut them, the aluminum honeycomb particles are small metal chips that fall directly onto the floor," said AdvanceTEC's Phelan. "When drywall gets cut, there are airborne particles, which do get wiped and filtered down, but a lot remain as latent particles that are everywhere, in the duct work, on surfaces, and on components." He said companies have told him that it can take five to six months to requalify if latent particles are found during validation. Once a room is qualified, installing a new piece of equipment or changing the configuration of a modular room is a cleaner process and adds to the cleanroom design's flexibility.

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Phelan figures about half of new facilities are modular, and he expects that figure to grow as biopharma takes to the just-in-time building and installation of modular systems. "Fewer people are on the construction site, so there is less contamination," he added.

The top surface of the modular ceiling panels is strong enough to bear weight from the floor above. That allows equipment, ductwork, and utilities to be installed in the overhead crawl space at the same time the cleanroom below is being built. "Sequencing the construction process can trim weeks to months," Phelan said of building a factory. The walkable ceilings also allow the facility to be serviced from above, reducing the contamination risk.

Added Loughran, "There is more assurance of the validation of the facility because it is built cleaner." He said the modules can be reconfigured more easily after a facility is built. Loughran said prefabricated modules allow a

biopharma company to delay the decision to move forward with a production facility for six months or more. "They can get through Phase II and be in Phase III before they pull the trigger for a production facility," he said.

Such modules played a role in late 2005 when Merck started expanding its West Point, Pa., roller bottle vaccine processing facility to meet market demand. The 38,000-square-foot expansion included 14,000 square feet of current good manufacturing practice space. Merck set a goal for the \$52 million project to beat its historic best 27 months to design and build the plant. Working with the consultancy IPS, it managed to complete the project in a record 24 months.

Merck built a 10-foot interstitial space between floors so that it could work on two elevations in parallel and keep very heavy building equipment from damaging the ceiling, said Steve Franey, RA, a technical architect at IPS who was senior project architect for the expansion. In a presentation at an International Society for Pharmaceutical Engineering conference, Franey and Merck's senior project engineer showed that the collaboration helped save six to eight weeks on the project, and the modular wall and ceiling system saved four weeks.

There is more demand for flexible and interchangeable facilities, but Hansz of FPR does not expect biopharma to go to standardized plug-and-play modules that any company can use. "They will always be tweaked," he said.

## Separating Humans from Machines



A cleanroom built using prefabricated wall modules has coved (rounded) corners, chemically cold-welded seams, and as few ledges as possible to reduce particle trapping.

Isolators made by companies such as Skan AG, Bosch, and Steris are also gaining popularity among biopharma as part of a trend to decrease the amount of cleanroom space needed. Isolators are an alternative to restricted access barrier systems (RABS). While RABS use an aseptic filter in a cleanroom, contamination is possible each time a door opens. Isolators are pressurized and use vaporized hydrogen peroxide (VHP) as a cleaning gas. The technology dates to the 1990s, when Lilly, Upjohn, and Merck used it with limited success; early systems required an 18-hour decontamination cycle, since improved to three hours using VHP.

IPS's Kline said the Food and Drug Administration prefers closed systems such as isolators, and companies using high-value active pharmaceutical ingredients (APIs) are once again eyeing them to protect their investments. "Folks were not making changes until 2002. Products were at \$1 to \$2 per vial. But biologics are \$100 per vial. They can't afford to take risks," said Kline. Isolator designs started in 2002 are just now up and running, and they are catching on, he said.

Piggybacking on that trend is the move toward disposable contact parts as an alternative to cleaning. "This is the latest trend in biologic API factories," said Kline. "The contact part is disposed of every run."

While isolators have a bigger initial price tag, running from \$9 million to \$45 million compared to \$1 million for a RABS, the overall cost to operate them is less, Kline said, pointing to a Merck study. The isolators prevent contamination and are less expensive to build than the traditional cleanroom. RABS need another \$5 million more of investment for aseptic air; with isolators, there is a lower bioburden to be filtered, Kline said.

With isolators in place at various stages of the biopharma process, Kline said clients are starting to talk about not needing separate filling and formulation rooms. Combining the two would decrease line losses on pipes, he said. "I haven't seen anyone do this yet, but we are discussing it with folks."

Nanoproducts, which can break through the cell wall, are on the horizon and bring new challenges. Kline said the FDA is looking at future contamination control for nanotech.

## Improving Processes, Communications

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Kraft, Hansz, and others see room for improvement in biopharma when it comes to communications among people involved in new factory design. "They need to build better relationships with support organizations, more of a partner than a vendor relationship," Kraft said, adding that there should be more openness in the biopharma corporate culture.

"We've been getting people from the marketing side involved," said Hansz. Adding marketing to the production, manufacturing, finance, and research staff discussions is a recent trend. "They can have input into the future product lines and what is involved. It gives a glimpse into what is down the road."

Bringing the disparate parties into one room can also reduce process steps and trim the amount of floor space required. One client was able to reduce 1,500 square feet of floor space, Hansz said. "They can rethink their processes and use automation effectively. And they can decrease the volume of contamination control spaces, decrease the amount of space in which equipment needs to be exposed to the clean environment."

Kline added that it is important to have all the people who represent the process or the product design around the same table, using a team approach for the project's conceptual phase. They should pick the project electives and must haves. "The challenge is being part of projects without that type of input. Sometimes a project is 50% to 70% done, and the people who occupy the room get into it too late," he said. "A cross-functional team early on is the key to success."

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