

CMO-grown Innovation and Technology Helps Pharma Industry Keep Pace

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Today's contract manufacturing organizations (CMOs) offer the latest in **technologically advanced equipment and innovative homegrown production processes**—breaking new ground on the road to producing the next generation of pharmaceutical products.

Not so long ago, big pharmaceutical companies turned to contract manufacturing organizations (CMOs) solely to achieve efficiencies in cost, capacity, and time-to-market, or to obtain a specific expertise not available in-house. Today, these factors still also play a role, but the most dynamic driver behind the use of CMOs in the pharmaceutical industry is now rapidly becoming the unique, innovative, and state-of-the-art process and production technology they offer.

Many CMOs have gone far above and beyond the immediate needs of their customers to create innovative homegrown processes and to implement the latest, technologically advanced equipment—technology that frequently surpasses that available at Big Pharma's own facilities.

Improved process tools

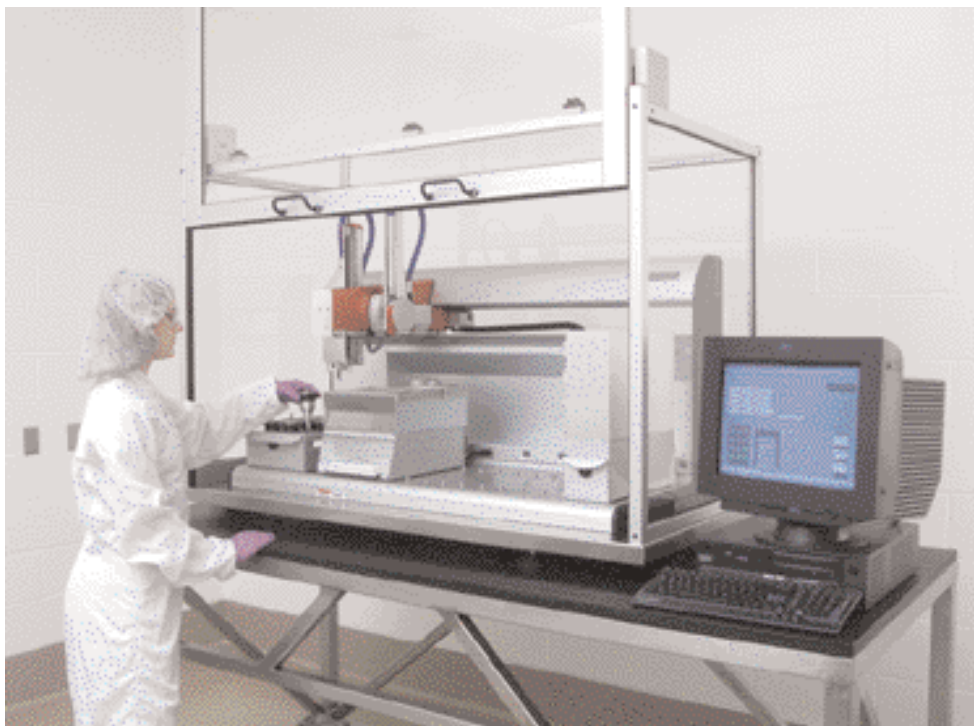
The total cost of pharmaceutical production includes not only the cost of building new plants. It includes the cost to maintain them, stay up-to-date on equipment advances, and to maintain a workforce of highly-skilled operators—operators with more than just the knowledge to run them, but with the expertise and experience necessary to continually update and improve them.

As the pharmaceutical industry moves deeper into the decade, the need to keep pace with next-generation process technology and process tools will only become more challenging—not only to meet increasingly tight cost-efficiency requirements, but in the case of many emerging pharmaceutical products, to make viable commercial production possible at all.

To meet this need, CMOs are already expanding and upgrading their existing plants, as well as building totally new, next-generation facilities. And, they're also investing heavily in outfitting them with state-of-the-art, highly-automated equipment. In addition, however, CMOs are applying their own expertise to advancing pharmaceutical process and manufacturing science and technology, contributing significantly to the development of new and innovative tools and systems.

One example of this innovation can be seen in the extent to which automation is being incorporated into CMO processes and operations. For example, Quintiles Preclinical and Pharmaceutical Sciences (Kansas City, MO) has implemented an automated robotic powder dispensing system that gives drug developers the flexibility to work with a broad range of drugs and dosage levels without having to perform extra formulation, analytical, or stability work. The completely validated robotic components can be used to fill either

QUINTILES



A scientist at Quintiles with an automated robotic powder dispensing system.

capsules or bottles and is fully automated, allowing it run overnight without human intervention.

Designed for small-scale clinical supply, the system can produce 60–100 capsules or bottles per hour and handle a variety of dosage levels such as 10mg, 30mg, 60mg, and 100mg capsules. “A computer can weigh things out faster and more efficiently than a human can,” observes Paul Skultety, vice-president for early development and laboratory services at Quintiles. The system automatically weighs each capsule, identifying and reporting any errors for rejection.

Quintiles has also invested in liquid-fill hard-gelatin capsule equipment that performs comparably to soft-gel equipment. Capable of filling 15,000 capsules per hour, the system incorporates an additional component that seals the capsules together to prevent leaking. As described by Skultety, the liquid encapsulated microspray sealing (LEMS) unit manufactured by Capsugel (Morris Plains, NJ), sprays the capsule with a mixture of water and alcohol. The spray is aimed at the point where the cap and body meet, dissolving a small amount of gelatin which, when dried, seals the cap and body together.

Althea Technologies, Inc. (San Diego, CA), has implemented two types of automated fill-and-finish systems—“Flexicon Monoblock FMB210” vial-filling equipment (Flexicon, Denmark) and an advanced syringe-filling system, “INOVA SV122” (Inova, Green Bay, WI). Alan Moore, Althea’s executive vice-president and chief busi-

ness officer, points to a number of benefits provided through their investment in automation—the first being speed. “The automated vial-filling system can fill approximately 60 vials per minute and the syringe system can fill 75 syringes per minute,” reports Moore.

Roy Musil, senior director of quality control at Althea, points to increased accuracy as another benefit provided by automation to both manufacturers and patients. “The ability to consistently fill an accurate volume of liquid means a more-accurate dose for the patient, while the use of pre-filled syringes also saves the client money.” Musil point out that with a vial system, each container holds a volume slightly over the recommended dosage, due to the fact

that it’s difficult for clinicians to extract the entire volume of liquid from a vial. In contrast, with automated systems producing prefilled syringes, overfilling is not necessary, and clients can save up to 0.1 or 0.2 mL per unit. “In the long run, when tens of thousands of units are filled, there are considerable cost savings,” notes Musil.

In addition, automated equipment also minimizes the amount of manipulation needed by technicians or operators. As Musil points out, “This both lowers the risk of product contamination and limits the exposure of operators to dangerous chemicals.”

Biotechnology-based pharmaceuticals. Biotechnology has become a particular focus area for CMOs as the number and variety of new biotechnology-based drugs, moving rapidly out of development and through the final phases of clinical trials into full-scale production, continues to grow. As described by Michiel E. Ultee, senior director of biopharmaceutical development and operations at Laureate Pharma (Princeton, NJ), “biotech-based products are growing at a rate almost twice that of conventional drugs.”

Though their arrival is certainly welcome to the industry as a whole, their unfamiliar and specialized manufacturing needs also present a number of new challenges for CMOs, who must not only provide the most advanced equipment and technology available to produce them, but also the expertise necessary to successfully implement and manage very complex and expensive processes. As pointed out by Ultee, “The development of the



An Althea Technologies laboratory technician with the Flexicon Monoblock automated vial filling machine.



A pilot-scale mammalian-cell bioreactor in operation at Laureate Pharma.

next generation of biotech-based pharmaceuticals will be very different from that of conventional small-molecule drugs.”

Ultee’s view was supported at the most recent national AAPS meeting in Salt Lake City, Utah, where, as observed by Norm Alworth, RPh, pharmaceutical manager at MPT Delivery Systems, “Among this year’s exhibitors were a host of companies presenting specific technology and products that didn’t exist in this industry five years ago.”

Gala Biotech (Middleton, WI), recently acquired by Cardinal Health, focuses its attention on monoclonal antibodies and gene insertion/expression technology. Gala’s Gene Product Expression or “GPEX” technology is aimed at rapidly developing highly expressive mammalian cell culture lines and their use for the production of recombinant proteins. The company recently established a 43,000-ft² facility in Middleton, Wisconsin, for GPEX-based cell line development and CGMP-compliant protein production.



Operators set up a mammalian-cell bioreactor in Laureate Pharma’s CGMP facility.

Gala’s GPEX technology is based on the use of “retrovectors,” which can be thought of as disabled retro viruses. Though retrovectors look like retro viruses, they don’t carry any of the protein-encoding genes of the virus, but rather the gene of interest (i.e. the gene for a monoclonal antibody).

The technology has reduced the time needed to develop a stable production cell line for a target protein from as long as 18 months to just five or six. Says Michael Jenkins, PhD, Gala’s director of business development and commercial operations, “In as little as three months, we can typically provide clients milligram-amounts of material from an unoptimized cell line. At the six month stage, we can provide a stable cell line in serum-free media at commercially viable expression levels” (see Figure 1).

Jenkins points to the high transformation efficiency of the GPEX approach, noting that virtually 100% of the target cells are transformed. “This is a significant advantage when compared to other methods of gene expression such as transfection or electroporation, where insertion frequency can be as low as one out of every 100,000 cells and which can require additional selection steps and the use of selectable marker genes,” says Jenkins. For bicistronic (and multicistronic) applications, GPEX allows multiple genes to be carried and inserted by a single retrovector, thereby increasing efficiency.

The GPEX retrovectors also target high-expressing chromosomal matrix attachment sites in the target cell genome, generating a higher expression of the gene in transduced cells and increasing yield. GPEX cell lines are also optimized via a repetitive insertion process that increases the number of inserted gene copies and proportionally increases target protein expression levels. The optimized cell lines may have a dozen or more copies of the desired gene, all of which are stably inserted and express the target protein. “With our

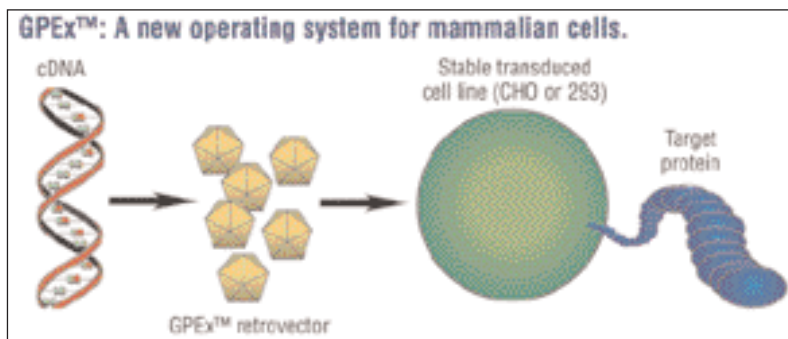


Surface samples are collected for environmental monitoring at Lancaster.

Figure 1: GPEX retrovector technology directs mammalian cell culture lines to efficiently produce recombinant proteins.

technology, both the heavy and light chain subunits are produced from a single mRNA molecule,” notes Jenkins.

Lyophilization. Concurrent with the increasing number of biotech-based pharmaceutical products entering commercial-scale production has come increased demand for freeze-drying, or lyophilization, capability. Since most proteins aren’t stable in solution or powder states, they must be dried prior to storage. However, most standard drying techniques can cause significant



RiboPrinter microbial characterization system.

damage to proteins, resulting in loss of potency. To deal with this, many pharmaceutical companies are using lyophilization to stabilize their protein-based drugs and improve their shelf life.

Because lyophilization is such a complex science, subject to close FDA scrutiny, many pharmaceutical makers choose not to attempt it in-house. As a result, it has provided a lucrative opportunity for those CMOs specializing in the capability, and who have made the significant investment necessary to ensure total FDA compliance. One example is Lyophilization Technology, Inc. (Ivyland, PA), which provides product characterization, formulation, and product design through the development of optimal freeze drying cycles. Says Wendy Sunderland, a research scientist at the company, “Since we’re very specialized in this one specific area, our scientists are extremely knowledgeable of the process and equipped to deal with any challenges that may arise.”

The company’s GMP-compliant laboratory houses seven pilot-size lyophilizers, as well as certified portable cleanrooms. The freeze dryers are equipped with automated control and data acquisition systems.

DSM Pharmaceuticals, Inc. (Greenville, NC) is another CMO actively investing in lyophilization technology. Not satisfied with off-the-shelf freeze dryer systems, DSM’s lyophilizers are custom-designed to its own specifications and incorporate control software developed in-house. “LyoAdvantage” software includes full critical component redundancy, and as described by Sholto Maclean, DSM principle scientist, “gives us extremely tight control of our process.”

Another innovative feature of DSM’s lyophilization systems is the use of liquid nitrogen as a cooling agent. According to Maclean, liquid nitrogen provides steadier, more-powerful cooling than



DSM lyophilization line. DSM's LyoAdvantage software tightly controls each cycle according to the optimum parameters established for each product.

standard compressor-based freeze drying technology, which can lose performance at low temperatures. "Our dryer shelves can be cooled to -65° , whereas standard compressors can only reach -50° or -55° ," says Maclean.

Liquid nitrogen also delivers more-aggressive cooling rates. Temperatures can be brought down at the rate of $2^{\circ}/\text{min}$, compared with the $1^{\circ}/\text{min}$ rate of conventional compressor systems. Since faster cycle times ultimately allow more cycles to be run per year, the approach can help increase productivity and lower costs. Also, because there are fewer moving parts in liquid nitrogen-based systems, they are more reliable and require less maintenance.

DSM's LyoAdvantage software tightly controls each cycle according to the optimum parameters established for each product which vary in terms of temperature, pressure, and time. Operators are

able to monitor all critical parameters including shelf temperature, chamber pressure, condenser pressure, vacuum system pressure, condenser temperature, and nitrogen flow. Detailed, computerized records are also kept on the settings used for each batch processed, which allow any problems to be quickly isolated. "If we run into a problem, we can resolve it in-house rather than call people in," says Maclean.

The use of automatic loading systems is another improvement over traditional methods. The equipment (custom designed by BOC Edwards Pharmaceutical Systems) automatically transfers packets of vials from the loading table onto temperature-controlled freeze dryer shelves, which are then transferred to the lyophilizer. The automated system provides a consistent vial-packing configuration within the dryer, which in turn provides greater drying consistency.

High-end analysis instruments.

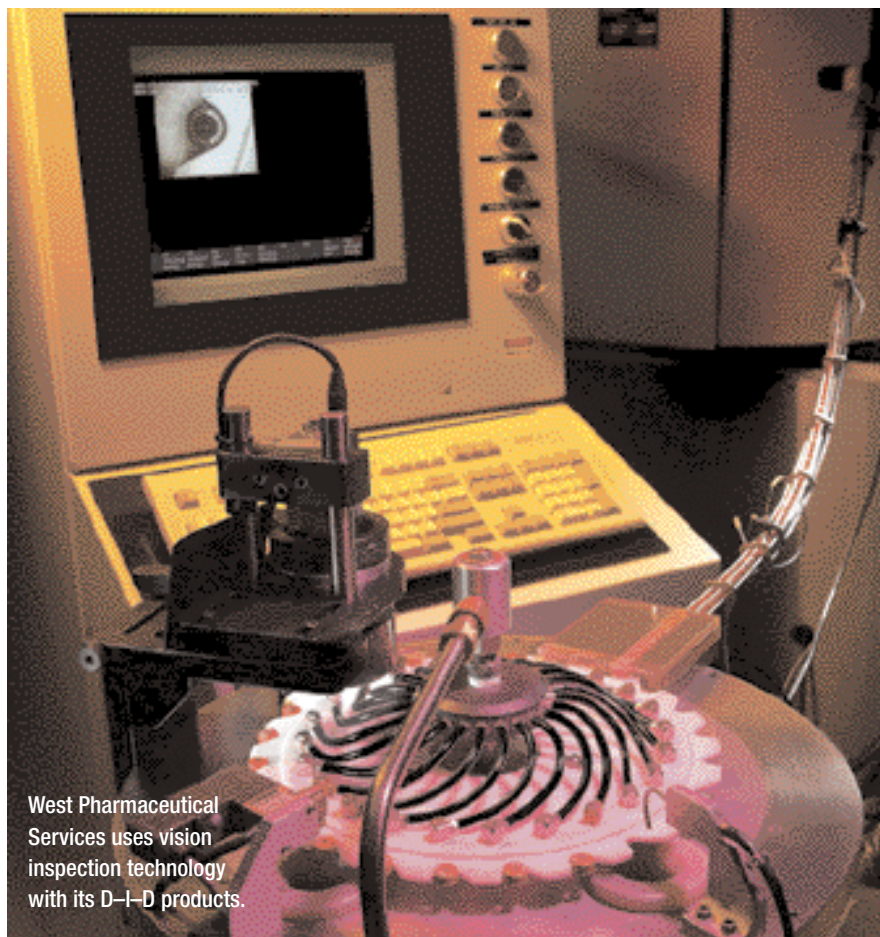
From API to dosage form to final packaging, highly-accurate and efficient testing and analysis have always been an integral part of pharmaceutical manufacturing operations. Today, however, with the FDA's em-

phasis on risk-based validation and compliance, and the industry's concurrent need to improve the cost-effectiveness of its operations, testing and analysis are taking on a whole new level of importance.

Once again, the need to invest in specialized equipment and experienced personnel have made contract organizations, and their testing laboratories, an important partner in the advancement of pharmaceutical industry technology and capabilities.

Lancaster Laboratories (Lancaster, PA) is one company that has invested in a wide variety of sophisticated analysis instruments. Lancaster sends its microbiologists to clients' sites to collect, package, and transport samples for analysis.

Among its contamination-monitoring tools is the "RiboPrinter" (DuPont Qualicon) microbial characterization system—a fully-validated piece



West Pharmaceutical Services uses vision inspection technology with its D-I-D products.

of equipment that tracks sources of contamination and identifies specific organisms. If contaminants are found in the facility or in a product, RiboPrinter enzymatically breaks up the DNA into fragments and then separates the fragments to obtain a genetic fingerprint of the source. An integrated database containing an extensive library of microbial genetic patterns is used to quickly compare and identify the contaminant organism. According to Tim Oostdyk, PhD, vice-president of technical operations at Lancaster, "The match is precise enough to identify the particular strain of an organism."

The entire process can be completed in less than eight hours, a major benefit to any pharmaceutical operation, that can then immediately set to work to identify the source of the breach.

Packaging. Pharmaceutical packaging may be the final stage, but it's also one of the most crucial steps in the drug development and manufacturing process. It is essential that pharmaceutical prod-

ucts remain sterile up to and during administration.

In addition to meeting FDA and EPA standards, depending on the characteristics of the drug product, packaging must address a vast array of requirements from sterility to strength to moisture barrier, as well as any number of aesthetic and ergonomic concerns. Once again, CMOs have taken a lead role in advancing the science.

One recent advance in pharmaceutical packaging has resulted from the need to improve tamper-evident closures and seals to combat counterfeit products. To address this problem, West Pharmaceutical Services, Inc. (Lionville, PA) has developed "decoration-identification-differentiation" (D-I-D) technology, that in addition to customizing closures, also ensures product integrity, reduces counterfeiting, and improves information presentation on labeling. The company manufactures a variety of seals and closures for bottles and vials.

According to Don McMillan, vice-

president of marketing at West Pharmaceutical Services, the most widely used type of seal incorporating D-I-D technology is its "FlipOff" seal. This seal combines a wraparound metal shell with an attached plastic button that protects the site of syringe insertion. By lifting the plastic button with one's thumb, the button is removed and access is permitted. Once this seal flips off, it cannot be reattached, and healthcare workers are typically instructed to not use a drug vial if the seal is missing.

Typically, D-I-D customization is performed by printing or molding and usually contains a company's name and logo. Another option is for manufacturers to print a tracking code on the plastic seals that is only visible under UV light, or to print point-of-use instructions on the aluminum seals.

Specialty requirements

In addition to providing advanced technology and systems to meet established production demand, CMOs are also frequently the best source for expertise and technology capabilities to address specialized or newly-emerging technology requirements. For example, EaglePicher Pharmaceutical Services, LLC (Lenexa, KS) has seen an increase

in demand for radiochemical-labeled pharmaceuticals, and are now offering a GMP suite to accommodate these products.

According to Steven Greenwald, PhD, project manager at EaglePicher, "We've been getting a lot of requests to manufacture radiochemical-labeled drugs, especially from start-up companies." Using radiochemical labeling, researchers can track the progress of a drug as it moves through the body to evaluate key performance attributes such as its absorption characteristics and duration.

As pharmaceutical science and technology continues to advance and change, CMOs expect they will continue to be in the forefront of new process and process tool development and innovation. They also plan to continue to invest heavily in the most sophisticated and capable high-end production equipment. In a sentiment echoed by all the CMOs interviewed for this piece, DSM Pharmaceutical's Maclean says, "We're ready." **PT**

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