

Beyond Syringe Filling

Final assembly, secondary packaging and the CMO

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AFTER TURBULENT TIMES, BETTER ECONOMIC forecasts provide welcome relief — and the opportunity to pursue new strategies as markets begin to stir. Case in point: the pharmaceutical and biotech industry. The latest IMS Market Prognosis™ indicates a fairly stable period of growth in the coming years, thanks in part to a dynamic market for parenteral drugs, like injectables.

The growth in parenteral drugs are due in large part to an improving economy and an increased focus on home-based healthcare. The combined forces of cost pressures, demographics and the availability of more patient- and user-friendly delivery systems are driving the home-healthcare trend. Indeed, many chronic illnesses, like diabetes and multiple sclerosis, must be treated regularly with injections, and insurance companies are becoming more and more reluctant to reimburse clinic or hospital costs if patients can self-treat at home. This, in turn, is creating a vigorous market for final assembly and secondary packaging of cartridges into pens or auto-injectors. These devices are becoming extremely sophisticated and allow patients and caregivers to administer medication very safely.

As the parenteral segment grows, so does the need to ensure ever greater safety measures to prevent counterfeiting, mixups and other errors. To rein in costs and meet the increasingly stringent demands of regulatory authorities, drug companies often outsource production to contract manufacturing organizations (CMOs). A CMO partner with experience and

state-of-the-art facilities can meet high quality and safety standards. Distinct from filling syringes, final assembly and secondary packaging carry their own separate set of regulations. Knowing what they are is crucial to selecting a suitable manufacturing partner.

Manufacturing with a difference

The FDA's *Current Good Manufacturing Practices for Finished Pharmaceutical Products* catalogs a broad range of packaging requirements that a CMO must follow. Validated processes are only one aspect. For the FDA, it begins with the facility itself: "Any such building shall have adequate space for the orderly placement of equipment and materials," read the guidelines, "to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination."

This straightforward statement is at the heart of all design considerations. First and foremost, a facility must be arranged in such a way as to permit one step to follow the next in a logical sequence. CMOs often have multiple lines and use each of them to package different products. Building separate, straight

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manufacturing lines ensures a clear servicing side and unequivocal procedural sequence. Each line should be separated by single-pane safety-glass walls to enable constant monitoring and help prevent mixups and cross-contamination. Automated doors at the beginning and end of each line enable easier servicing and are best suited to a fully automated system.



Separating several lines using single-pane safety glass creates stable boundaries and allows for a clear overview of operations and the machines at the same time.

Pesky Particles

Human beings are the source of most contamination. They generate about 100,000 particles per minute: unacceptable in a sterile environment. Preventing the problem is a chief concern when constructing a packaging facility. As personnel and material move through the facility, a system of airlocks can be used to keep particles out of classified areas. Airlocks can also serve as changing rooms. Gowning procedures are nearly the same as for entering a cleanroom. Staff members wear shoes, trousers, shirts and gloves. Hair and beards are enclosed in nets. For the procedure to be effective, employees must follow rigorous and well-defined steps.

Finally, it is important to determine who has permission to enter the classified area and how to enforce security. One option is server-supported access control. Authorized staff use key cards that would give them access only to the area where they will be working. New access codes can be generated by software on a daily basis.

Peripheral Necessities

In addition to proper layout, a CMO must design other safety-oriented features into the blueprint. The most obvious is sheer space. Providing an area large enough to move about in com-

fortably can prevent accidents that might occur if people, products and machinery are too congested. Work surfaces also need to be ample enough to allow staff members to use and maintain a clear view of items placed on them. Employees take extraordinary care to avoid spills and breakage. Clearly posted signage that identifies machines and work areas help prevent confusion by staff members.

Maintaining appropriate environmental conditions is crucial in a packaging facility. Cartridges assembled into auto-injectors or pens must be kept in temperatures ranging between 59° and 77° Fahrenheit. Set point is at 71.6°. Ambient humidity must be kept in the 40% to 60% range, with the set point at 45%. Besides state-of-the-art climate control, a high-performance ventilation system must be installed to provide air for the laminar flow system, which is needed to create cleanroom conditions and draw out any contaminants. Experience shows that the air in the critical areas must be replaced completely at least five times per hour for maximum effect. Such technical infrastructure — including the supply systems for various utilities — are seldom in full view. Nevertheless, they must be easily accessible for cleaning and repairs. A top-of-the-line packaging facility will also have redundant systems as back-up in the event of an emergency. A ceiling built of sealed metal panels will allow maintenance personnel to service the supply systems concealed in the ceiling without interrupting production.

The Nitty-Gritty

No part of the design of a filling or packaging line can be left to chance. Function and cleanliness must be the guiding principles at all times. The material chosen for walls, floors and ceilings, for instance, should be particle-free and smooth. This makes dirt more visible and therefore easier to clean. PVC flooring, especially where blister packaging is performed, pro-



For a logical sequence of the individual steps, the best solution is a packaging line built in a straight line. Having a clearly defined service side avoids errors.

fects product integrity. PVC is less likely to generate static electricity, which can adversely affect highly sensitive drugs.

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Should a CMO wish to serve markets where a high level of cosmetic integrity is a must, additional care is necessary to prevent the introduction of fibrous materials. Staff must wear rubber gloves.

The Machines

The human factor in contamination has driven the effort to develop fully automated lines. Each CMO must ultimately find the right system for its needs. In syringe filling, for example, the restricted access barrier system (RABS) has become the state-of-the-art, because it prevents contact between people and the product. In final assembly and secondary packaging, automation limits human-product contact. Using a high-

ly technical, extremely precise mechanized system all along the line, a tray of injection systems is conveyed to a machine that applies labels, then to another that installs plunger rods. After that, another machine installs backstops, followed by the blistering machine and cartoner, which also packs the inserts.

Complete automation reduces the risk of contamination to a minimum. If a higher level of cosmetic integrity is required, a laminar flow system can be installed for blistering, which will prevent fibers from entering the blister packs. As a final note, storage and classified areas should be kept separate.

In the parenterals market, the home healthcare segment is showing strong growth potential. For a CMO prepared to meet the challenge, serving that market with complex systems like pens or auto-injectors presents significant appeal. However, building specialized facilities to assemble and package these devices takes considerable investment, since it demands sophisticated design and state-of-the-art technology. Meeting tough regulatory standards by the FDA and other international authorities is also a hurdle.

In the long run, though, forward-thinking strategies of CMOs support their clients to prepare for the changes – and opportunities – that lie ahead. ■