Considerations for Aseptic Filling of Parenterals

A CMO Perspective

by Keith A. Smith

Careful planning, innovative machine design, and rigorous attention to detail will assure maximum product delivery and minimize timelines from project initiation to completion. By the time a parenteral product arrives at our facility for filling, a client has invested considerable time and significant resources in its development and manufacture. Our experiences clearly demonstrate the importance of planning and attention to detail for achieving a filling run that enables that product to move efficiently to testing or market, helping to realize the greatest value from the client's resource commitment.

A 2,000-L bioreactor

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Key Initial Considerations

Without question, time spent on planning, particularly at the outset of a project, will be time saved in efficient completion of a filling operation. For a CMO, key variables at this stage are knowledge of a product's physical characteristics and its intended market. The CMO uses this knowledge as the basis for recommending the most appropriate filling equipment, delivery system, and container–closure system.

Knowing the market will suggest appropriate types of containers and stoppers as well as filling room and capping room environments. Products with unusual physical characteristics may require modifications of the filling system. For example, a different style of needle and/or a slower dispensing volume might be required for a viscous or foaming product.

Knowing a product's characteristics enables efficient performance of one or more media fills for product simulation and testing of filled vials for container closure integrity. Such knowledge also provides an excellent guide for determining the duration of the product fill. This, in turn, enables monitoring personnel, inspection personnel, and labeling personnel to plan for the most efficient use of their time.

Knowing the components to be used in the filling operation also enables a CMO to correctly validate component cleaning equipment.

Product Characteristics Influence Filling Machine Selection

The CMO will need to consider a product's physical characteristics, such as solubility, viscosity, and tendency to foam. It addition, the CMO should know the product's sensitivities to light and temperature, whether it is a solution, an emulsion or a suspension, and whether it is delivered in an aqueous or nonaqueous solution.

Product physical characteristics may suggest selection of one type of filling machine over another. For example, a stainless-steel syringe-type filler, rather than a peristaltic filler, might be more suitable for a nonaqueous product that is incompatible with silicone tubing. Specialized tubing may be required for a filling system if a client's product is incompatible with the type of tubing it typically uses. A system may need to be adapted to maintain stirring of a suspension or emulsion throughout the fill to ensure product homogeneity.

Product Characteristics and Vial Selection

A product's characteristics also dictate the container components selected for it. Components are the vial, stopper, and seal used in the product container system.

The product's fill volume will of course dictate the required vial size. If a radiolabel compound or other addition to the filled vial will be required, a larger vial will be needed to accommodate that additional volume. Other selection considerations may include the following:

- Specialized glass may be needed to ensure stable pH for an unbuffered solution or to reduce product binding to the vial when the concentration of active product is extremely low.
- Where low fill volume is an issue, a vial with a conical bottom may be desirable.
- For light-sensitive products, an amber vial may be a better choice than a clear vial.

Vial selection can also be influenced by target market considerations. For example, a vial may have to meet compendial requirements such as US Pharmacopeia (USP) and/or European Pharmacopoeia (EP) testing for Type I borosilicate glass.

Product Characteristics and Stopper Selection

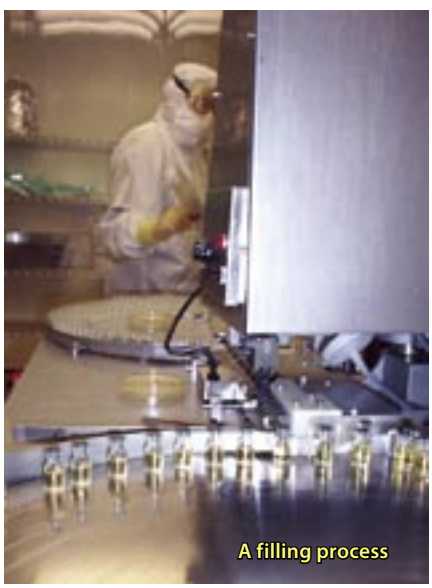
Considerations for stopper selection are similar to those for selecting a vial: The product's physical characteristics and its intended market influence selection criteria.

Depending on the market where the product will be distributed, selection considerations may need to focus on meeting USP, EP, and/or Japanese Pharmacopoeia (JP) compendial requirements.

Stopper size will need to match the finish of the selected vial. Compatibility of the product with the stopper's rubber formulation will dictate the stopper's physical characteristics. For example:

- A mineral-oil–based product will be incompatible with a butyl rubber stopper; a neoprene stopper is a better choice.
- When a client requires filling of a low concentration product, a fluoropolymer-coated stopper may be most suitable to reduce adsorbance of the product to the stopper's surface.
- When potential stopper deterioration is a consideration — because of long-term exposure to a product with a high or low pH, for example — a fluoropolymer-coated stopper may be the best selection.

Availability and delivery lead-times for selected components become vital issues, especially to avoid delays to market as a product moves to commercial distribution. They are particularly important considerations when large numbers of fill units will be needed. The vial and stopper should be selected before a product stability program is begun: Any change in stopper specifications will delay completion of the filling operation until stability validation of the new specification can be completed.


A filling process

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Selecting the Appropriate Seal

Because the seal does not contact the product, its composition is not as critical as other component-selection criteria. The appropriate seal must be suitable for the container system on which it will be used, and it must ensure system integrity. Assurance is most often achieved through a microbial ingress and/or a dye ingress container integrity test in combination with a long-term stability program.

The most common seal style is a colored plastic button that a user pops from the top of the vial to expose the stopper. A less common seal design is also a pop-off plastic button, but it offers a user the option to tear away the seal to fully expose the top of the vial.


A Cozzoli fill-line

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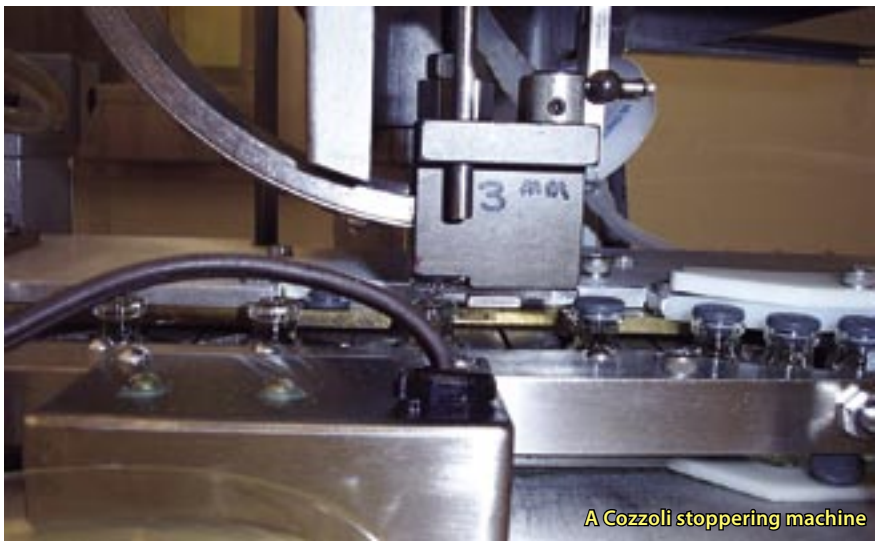
The color of the seal, although certainly not critical for product or container integrity, may play an important role for specific client marketing or product identification. The color may have been commercially designed to identify a kit component, or it may identify a particular product line or dose, or it may be a universally recognized color for a specific product (for example, the color black identifies potassium chloride solutions).

Validation and Cleaning

After the container system has been specified, the next steps are validation of the vials and of the cleaning, sterilization, and depyrogenation processes.

Vial Cleaning: Vials are most often validated using a salt spike test in which they are spiked with a known quantity of sodium chloride. Positive control and negative control vials are reserved, and spiked vials are randomly distributed throughout a wash load of vials. They are washed by standard operating procedure, and then those that were marked as spiked are removed from the washed load. Stoppers follow a similar procedure.

Sterilization of Stoppers and Filling Equipment: A validated autoclave is used for sterilization following a


A Cozzoli stoppering machine

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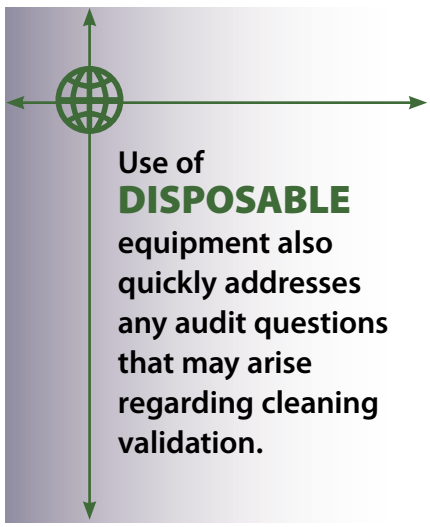

validated load pattern and process cycle. For validation, the load is well-defined, although some minor variation is permitted. For example, filter types and filtration tubing lengths may vary. For the highest levels of assurance, a validated cycle using worst-case scenarios is recommended, such as using the largest filter housing with the longest lengths of tubing.

Development Autoclave Load-Testing: At our facility, testing — using both thermocouples and biological indicators — compares several worst-case loads to loads using shorter tubing lengths and the smallest filters; results demonstrate that these cycles meet or exceed validation criteria. Testing includes less-than-full loads, such as processing a second length of tubing by itself. In this case, materials to be processed are placed in the same autoclave location as the location assigned in the full load.

Autoclave runs are performed, varying the sizes of stoppers — for example, 13 mm diameter and 20 mm diameter — as well as the quantity of stoppers in the load. Testing in our facilities covers up to 10 packs of stoppers per load with not more than 1,000 stoppers per pack, whether 13 mm or 20 mm size. Stoppers are gravimetrically counted as they are packed to ensure that the 1,000-stopper limit is not exceeded.

Depyrogenation of Vials uses a depyrogenation oven, a defined batch load, and defined time and temperature parameters. After vials are washed, they are placed in stainless steel pans for depyrogenation. Validation at our facility is based on the mass of the load, to allow flexibility for varying vial sizes and carboys. For each depyrogenation cycle, vial types are defined, as are the pans in which each vial type is placed and the filled weights of the pans. Each carboy size and weight is defined, and the weight of vials and carboys in the load is calculated to ensure that the sum does not exceed the validation mass limit.

Disposables Save on Cleaning of Product-Contact Parts: Our facility addresses the issue of cleaning of product-contact parts by using only sterile, new parts for each fill. For some products, a glass carboy is used to hold the bulk for filling, but the used carboy is discarded after each fill. Most products are filled at our facility using a sterile, endotoxin-free low-density polyethylene bag in lieu of a more traditional glass carboy or stainless steel tank.

Tubing used to transport bulk product to a bulk vessel, from a vessel to the filling machine, and from a filling machine to a needle are all discarded after use. Silicone tubing is most often used, although fluoropolymer tubing or double-extruded tubing is another option. All tubing that contacts the product is discarded after use. Other items are also discarded, such as tubing connectors and filling needles.

The cost of product-contact equipment is generally a small percentage of the total manufacturing cost for bulk filling, including the cost of raw materials and labor. The time saved by not needing to validate cleaning effectiveness for product-contact parts reduces preparation time needed to move a product along a timeline. Use of disposable equipment also quickly addresses any audit questions that may arise regarding cleaning validation.

Simulated Media Fills

Up to three product-simulating media fills are performed using the same container system filled with the same or more volume as the product volume. For early-phase products, one product-simulating media fill is performed before product is filled for the first time, and the second and third media fills may occur shortly thereafter. In each fill, the vials, stoppers, seals, and filling equipment are the same as those used for the product. For early-phase products, the first media fill must pass incubation testing, growth promotion tests of the incubated vials, and container integrity testing before the first product fill. For late-phase products and commercial products, successful incubation, growth promotion, and container integrity must be complete for three consecutive media fills before the first product fill.

Maximizing Product Use in a Filling Operation

The highest consideration is to minimize product losses. A filling machine designed so that product is withdrawn from the bottom of the bulk vessel, carboys, and bags will minimize the risk of drawing air into the lines and thus minimize residual waste. Positioning the bulk vessel to be lower than the filling machine assures that bulk product is always drawn upward. Empty filling tubing is purged of air by positioning the filling needle at the highest point, thus assuring that the air is always being displaced by a product front entering the filling lines. Product pumped through the filling lines is collected and saved. The purge process and purged product collection are managed through process design.

Machine design also can minimize the volume of bulk lost during filling set-up to just two or three vials — rather than a dozen or more, as is often the case — by means of a table that provides coarse filling pump settings. Once the coarse setting is adjusted, it is verified using water for injection rather than product.

How a Broader Fill Range Saves Time, Reduces Wasted Vials

The fill tolerance for dispensed volume can be established to allow some variation in the actual volume dispensed. As an example, for a filling machine with an accuracy of ±2% of its setting, the fill tolerance may be set to ±5% of the target fill volume. This broader fill range greatly reduces the quantity of filled set-up vials required to bring the fill volume into range, from as many as 50 or more for a very tight fill range to only two or three vials for the broader range. Broadening the tolerance also reduces the time required to adjust the fill volume, from as many as 45 minutes to around 15 minutes, thus lowering the length of time the product remains in the filling room.

This broader range does not significantly reduce the quantity of vials filled. For example, consider a filling operation specifying 8 L of bulk to be filled at 2.00 mL/vial. Theoretically, this will produce 4,000 vials, but for a machine with a ±2% fill range to achieve that exact 4,000 count, it will have to be set to dispense exactly 2.00 mL/vials, so that taking the ±2% accuracy of the filling machine into account, no vial will fall outside tolerance. However, a mechanic will use at least 50 vials of product to ensure that the machine dispenses 2.00 mL/vials, which means that 50 product vials will be lost, and the actual filled vial count will be not more than 3,950.

If the tolerance is broadened to ±5%, a mechanic is likely to use no more than two vials to adjust the machine to dispense 2.06 mL/vials. At that dispensed volume, 8 L of bulk will yield 3,883 vials minus the two vials used during adjustment, or 3,881 vials. While this quantity is 69 fewer vials than the expected quantity of 3,950 for the tighter ±2% tolerance, it is also 48 fewer rejected vials and it represents a setup time-saving of at least 30 minutes, reducing the amount of time that product must spend in the filling room.

Filling is the final operation during which a client's bulk product is manipulated. It brings to fruition all the effort and cost of manufacture. It is also the phase with the highest risk, not only because of the value of the product, but also because it is the last opportunity to ensure product integrity before it is apportioned for patient use. Careful consideration of component selection, careful validation and testing, careful machine design, and careful attention to detail in the filling operation itself will maximize the volume of product delivered for clinical or commercial use and minimize the amount of time between initiation and completion of a filling project.

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