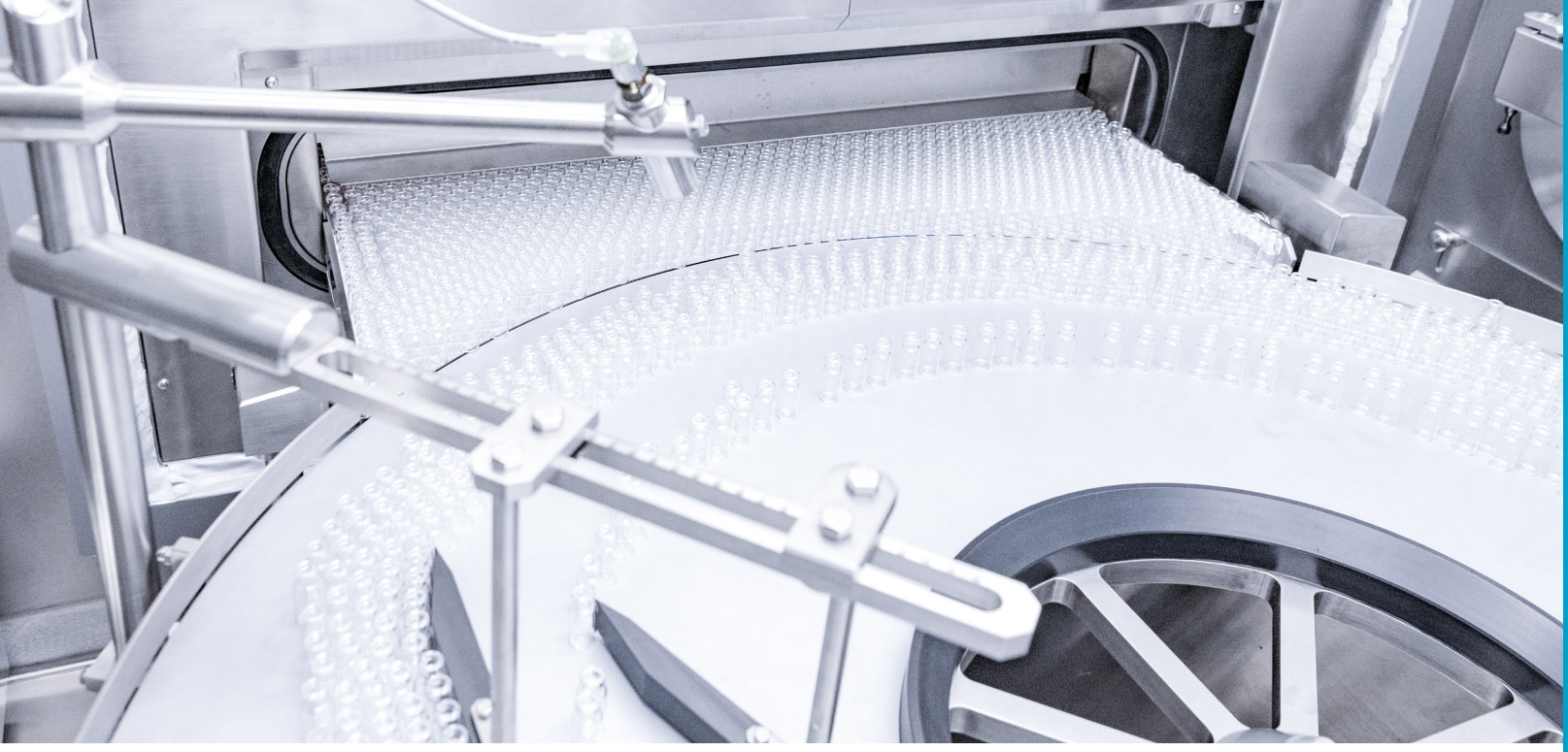


May 2023

# Key Considerations for Selecting Fill/Finish Manufacturing Technologies

Eleftherios Hristofas
Manager, R&D Pharma Processing

## Executive Summary

With the growing pipeline of biologics, increase in vaccine production, and trends toward smaller batch sizes targeting smaller patient populations, there is increasing demand for advanced manufacturing technologies. These parenteral drugs require advanced facilities and equipment for fill/finish operations to ensure product quality and safety. As pharmaceutical, biotech companies, and contract development and manufacturing organizations (CDMOs) look to build or expand manufacturing capabilities, there are several factors that need to be evaluated: maximization of floorspace, reduced risk of cross-contamination, manufacturing flexibility, varying throughput, tech transfer, and various primary packaging formats. Today's fill/finish equipment technologies present various options to meet many of today's manufacturing requirements. For example, **flexible fill/finish technology** lends itself well to variable size batch production (scaling from clinical to commercial) in multiple format presentations (vials, syringes, and cartridges). Flexible fillers are beneficial to developers as they maximize production floorspace, produce high quality batches, and provide the flexibility to launch with different delivery presentations from vial configurations to pre-fillable syringes to combination devices.

West recognizes the important role that fill/finish original equipment manufacturers (OEMs) play in the drug developer's value chain. We continue to partner with these OEMs by incorporating feedback from them as new primary packaging systems are being developed to ensure the products can be handled, filled, and processed for their intended use. Collaboration with OEMs allows the packaging development and fill/finish line development to align, ensuring ease of product introduction into future line builds. By working with the OEMs during the component product development phase, key requirements on how to successfully complete the fill/finish process with specific container closure components are understood, providing a jump start on the fabrication of new lines, change/format parts, or implementation into existing fill/finish lines. While this scope of work is early in the packaging component development phase, the collaboration de-risks the manufacturing process steps as the components get adopted and move to the clinical and commercial scale.

By obtaining information and proactively mapping out your approach early to better understand the decisions you need to make around your fill/finish strategy, you can avoid the risk of making an investment in equipment or processes that may not meet your long-term needs.

When purchasing and designing a fill/finish line, some of the critical areas that need to be considered upfront to streamline the equipment build process are:

- Restricted-Access Barrier System (RABS) vs. Isolator
- Line Speed
- Component Introduction
- Format Parts
- Packaging Removal
- Container Transport Mechanism
- Closure Defect Prevention
- Pump Mechanism
- Wetted Path
- Vacuum Filling
- Number of Dosing Stations
- Dosing Accuracy Verification
- Inert-Gas Purge Capability
- Plunger Placement Capability
- Number of Stopper/Plunger Placement Stations
- Electrostatic Reduction
- Particulate Control and Monitoring
- Material Out-Flow
- In-line Inspection and Rejection
- Automation and Data Management

## Restricted-Access Barrier System (RABS) vs. Isolator

When choosing between a RABS versus an isolator, you must consider protection of the drug product from outside contamination, protection of the manufacturing personnel from exposure to the drug product, the initial cost of the equipment, and operational costs associated with supporting the installed equipment (e.g., gowning, microbial sampling, and cleaning and decontamination costs).

1. RABS separates the filling operations from the operations personnel and the manufacturing room, but it doesn't fully isolate the filling operations from the manufacturing room. Typically, a RABS is installed in an ISO 5/Class 100/Grade A/B environment, and any personnel in the room need to be gowned for aseptic manufacturing. Monitoring of the aseptic status of the room and the operators (for example, by microbial sampling) is required during manufacturing operations. If an operator is required to make an intervention to correct an unexpected issue, the operator must work through the glove ports of the RABS. If the door to the RABS is required to be opened in order to address the issue, then when the corrective action is completed, a simple wipe-down of the RABS may be sufficient without performing a full decontamination cycle.

2. An isolator fully isolates the filling operations from the operations personnel and the manufacturing room. While the environment inside the isolator is maintained under aseptic conditions, the manufacturing room may be maintained in a lower-level classification, such as ISO 7/Class 10,000/Grade C, and under non-aseptic conditions. The operators may be gowned in scrubs as opposed to aseptic gowning, and they don't need to be monitored for microbial contamination. If an operator is required to make an intervention to correct an unexpected issue, the operator must work through the glove ports of the isolator. If the door to the isolator is required to be opened in order to address the issue, then when the corrective action is completed, the isolator must again be decontaminated. If contingencies are not in place to enable isolation of the drug product and the container/closure components, opening of the isolator doors can result in significant product yield loss or complete loss of the batch.

*Vial filling and stoppering machine within a RABS enclosure. Note the opening above the RABS enclosure. The RABS enclosure is placed underneath filtered unidirectional air flow which is commonly provided by a separate air-handling unit. In order to allow the air to flow out of the RABS enclosure, the doors of the RABS enclosure have openings at the bottom. In this image, these openings can be seen guarded by stainless steel bars. Although not shown on this image, RABS enclosures may be outfitted with glove ports to allow the operator to make manual interventions without opening the RABS doors. Image courtesy of Bausch+Ströbel. Used with permission.*

*Vial filling and stoppering machine within an isolator enclosure. The air-handling capability of the isolator is integrated into the isolator unit. In contrast to the RABS doors, the doors of the isolator are thicker and are fully sealed, typically by inflatable gaskets, against the door frames of the isolator. The image also shows two glove ports on each door, which allow the operator to make manual interventions without opening the isolator doors. Image courtesy of Bausch+Ströbel. Used with permission.*

## Line Speed

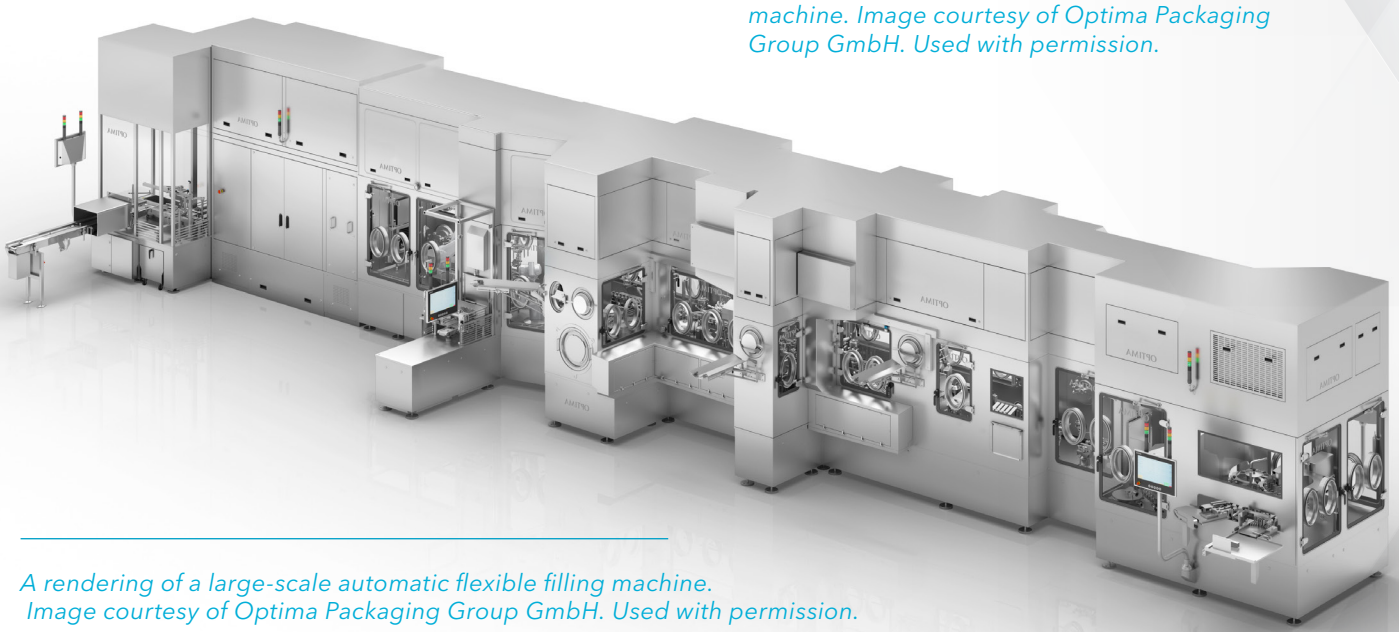
Generally, the fill/finish line should be of sufficient finished-product throughput such that it can perform fill/finish of the entire formulated bulk drug product within the time the product is allowed to remain in bulk format or to be out of refrigeration, and within the timeframe which is able to be supported by the available shifts of operations and supporting personnel. The offerings from fill/finish OEMs range from the laboratory-scale semi-automatic benchtop systems (roughly 100 containers per hour) to very large fully automated systems that can exceed 40,000 containers per hour.

Here are several questions you need to answer that could impact the speed of your filling line:

1. What is the volume of the bulk drug product?
2. How long is the formulated bulk drug product stable prior to filling into the final container and subsequent storage?
3. What percentage of the batch will undergo in-process fill weight checks (IPC)?
4. How many shifts of operations and supporting personnel are anticipated for manufacturing operations?
5. What portion of the fill/finish operations are to be performed manually vs automatically?

*Benchtop-scale semi-automatic syringe filling and plunger placement machines. Image courtesy of Bausch+Ströbel. Used with permission.*

*A rendering of a small-scale automatic flexible filling machine. Image courtesy of Optima Packaging Group GmbH. Used with permission.*



*A rendering of a large-scale automatic flexible filling machine. Image courtesy of Optima Packaging Group GmbH. Used with permission.*

## Component Introduction

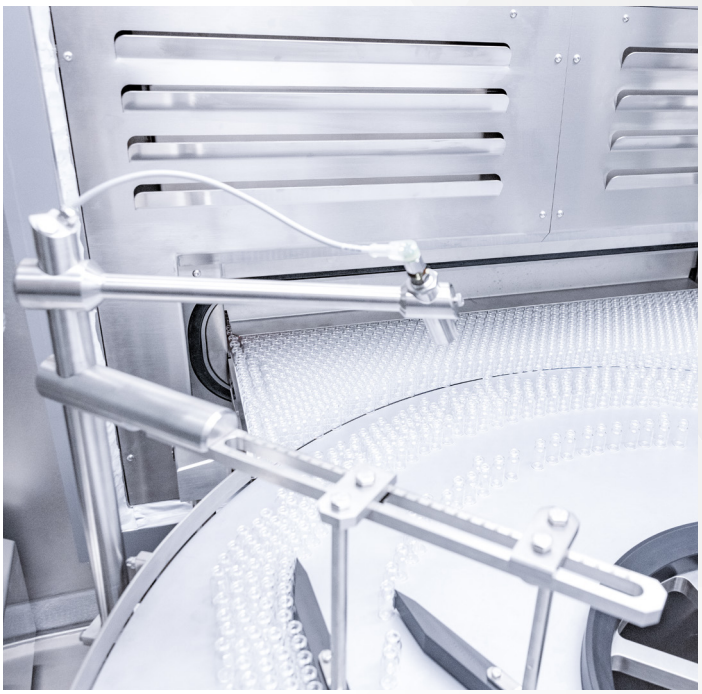
Containers and closures may be packaged as either ready-to-use (RTU) sterilized, ready-to-sterilize (RTS), or require washing and sterilization. RTU components reduce or eliminate the need to maintain in-house washing and sterilization equipment, subject-matter-expertise, as well as the ancillary clean utilities which are needed for performing washing and sterilization. Containers can be introduced in nested packaging formats or bulk/tray formats. Containers in nested formats are usually aligned with ISO 11040-7, ISO 21881, or ISO 21882, and are usually available as RTU. Containers in bulk format may be RTU, RTS, or may require washing and sterilization/depyrogenation. Closures and seals have traditionally been available in bulk packaging format, as RTU, RTS, or requiring washing and sterilization. Bulk packaging sizes can range from a few hundred components per bag (small sterilized or sterilizable bags), to several thousand (sterilized or sterilizable ported bags), or much larger volumes (non-sterilizable bags of bulk components). More recently, some fill/finish OEMs have introduced technologies to process nested closures or nested snap-on seals, which is driving component suppliers to offer closures and seals in nested format as well.

Rapid transfer ports on isolators are moving from traditionally manual operation to automated operation, which allows ported bags to be used with fewer ergonomic challenges and contamination risks compared with manual operation.

Some areas to consider for closure introduction include:

1. **Is the enclosure a RABS or isolator?** Most isolators are generally outfitted with rapid transfer ports and utilize ported bags for closure introduction, though there are some isolators that can process nested closures. RABS may also have rapid transfer ports, but can also be equipped with material transfer modules that enable aseptic introduction of closures.
2. **What is the batch size?** Smaller bags for larger batch sizes require more frequent operator interventions to introduce components. Ported bags may be a more effective option. There are also larger equipment that can wash, sterilize, and introduce closures directly into the fill/finish line.

*A tub of nested, sterile, ready-to-use containers, just prior to tub opening / lid removal. Image courtesy of Optima Packaging Group GmbH. Used with permission.*



*Washed and sterilized bulk vials coming out of a depyrogenation tunnel and accumulating on a rotary table prior to filling. Image courtesy of Optima Packaging Group GmbH. Used with permission.*

## Format Parts

Consideration should be given to how the equipment may be used in the future. While the equipment can be designed to process a single container format (for example, a 10R vial), is there any desire for the equipment to be designed to accept format parts and process other container sizes, such as other vial sizes and packaging formats, such as pre-fillable syringes or cartridges?

## Packaging Removal

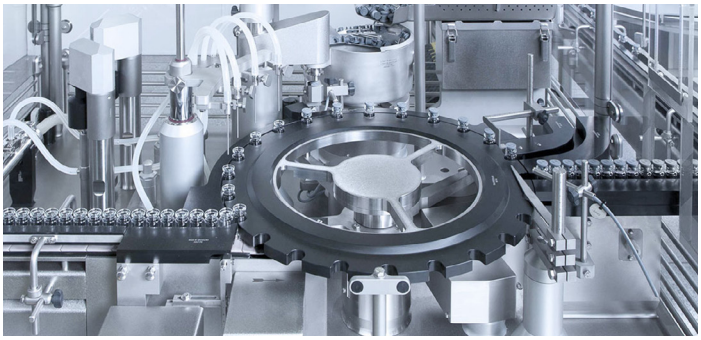
Containers can be introduced in nested packaging formats or bulk/tray formats, which include secondary and tertiary packaging around the containers. For example, a nested RTU container is supplied in a nest and tub configuration with an insert liner and sealed lid which serves as a microbial barrier but is permeable to sterilizing gases. This tub assembly is packaged within sealed bags. The process of removing this packaging depends on the fill/finish room and line layout.

1. Manual removal of packaging layers, such as having an operator cutting the bags open with scissors while working through glove ports is generally cumbersome and not feasible beyond small batches.
2. Semi-automatic removal of packaging layers combines some automatic processing with operator-assisted actions and interventions. For example, the operator may be required to manipulate the packaging and present it appropriately to the bag opening equipment, after which the automated equipment performs the bag cutting and opening operations.
3. Fully automatic removal of packaging layers is the most efficient for the operator, as it limits the required operator actions to feeding the package into the equipment, and if needed, intervening when the automated equipment doesn't operate as expected.

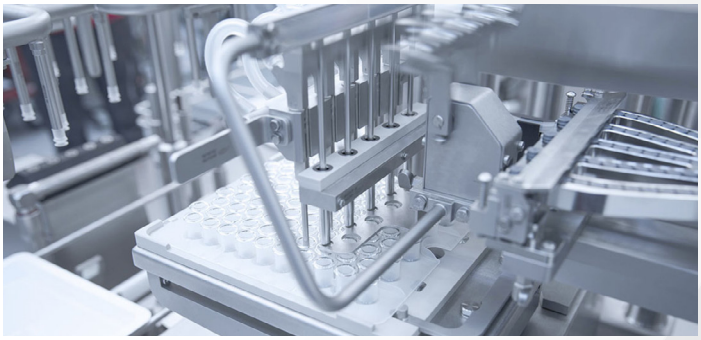
## Container Transport Mechanism

The manner in which the containers are manipulated and transported by the equipment plays an important role in attributes such as line speed, particulate generation, and the ability to perform 100% in-process [weight] checks (IPC).

1. Robotic pick-and-place transport methods, where individual containers are picked up by robotic grippers, tend to be slower than conveyor transport methods, though they also tend to be better compatible with polymer containers, as they minimize or eliminate the friction and potential abrasion that occurs between the container and the conveyors. Robotic transport methods also enable 100% IPC.
2. Conveyor transport systems, where all containers are moved via conveyors, generally enable faster line speeds, though in-process weight checks may be limited to a small sampling of filled containers. Additionally, because of the inherent friction involved in moving containers via conveyors and ancillary feed screws and guide rails, there are increased risks for the occurrence of abrasions, scratches, and particulate generation. Materials selected for construction of the conveyors, feed screws, and guide rails need to be checked for suitability for processing the associated containers.
3. Some OEMs have introduced hybrid transport methods, where containers are moved through the fill/finish process in a conveyor of grippers or comb-like fixturing, which combines the benefits of robotic handling (lower abrasion, 100% IPC) with high-speed throughput.
4. Finally, for nested containers, some machines perform filling and closing of the containers as they reside in their nests; the containers are not removed from their nests. The technologies also combine the benefits of lower abrasion and 100% IPC with high-speed throughput.



*Filling and stoppering of vials through a conveyor-based transport system. Image courtesy of Bausch+Ströbel. Used with permission.*



*Filling and plunger placement of nested pre-fillable syringes as they reside in their nest. Image courtesy of Bausch+Ströbel. Used with permission.*

## Closure Defect Prevention

Similar to the risks of abrasion, scratches, and particulate generation for containers, a similar risk exists for the handling of elastomeric closures. Traditionally, vibratory sorting bowls and feed tracks are used to orient, arrange, and feed elastomeric closures to the point of closure placement. Whether the closures are transported on the drug-contact side or on the non-drug-contact side, it is necessary to ensure that particulates are not generated during the vibratory sorting and feeding process. The risk of particulate generation may be reduced or largely eliminated by implementation of the following:

1. Reducing the intensity of vibration.
2. Reducing the time that the closure is exposed to vibration (for example, by stopping the vibration when there is not an immediate need to feed closures).
3. Reducing the length of the vibratory feeding track.
4. Transporting the closure on its opposite side (for example, rather than transporting a plunger on the bare rubber non-drug-contacting surface, instead transport it on its laminated drug-contacting surface, if the plunger is laminated).

Any contact between the sealing surfaces of an elastomeric closure and the fill/finish equipment (such as vibratory feeding systems, vent tubes, closure pick-and-place equipment, etc.) should be verified to not cause any damage (such as scratches or abrasions) to the sealing surfaces of the elastomeric components, as such damage may adversely impact the sealing performance of the closure and compromise container-closure integrity (CCI). This is especially important for laminated closures, as the laminations tend to be composed of rigid polymers rather than elastomers.

## Pump Mechanism

There are three main types of pump mechanisms that can be utilized to dispense liquid drug product:

1. A peristaltic pump is a positive displacement pump which moves fluid through flexible tubing, such as tubing made from silicone. No parts of the peristaltic pump contact the drug product, thereby enabling single-use / fully disposable filling.
2. A rotary-piston pump is a positive displacement pump which uses a piston to take in drug product through an intake stroke, and to dispense it through a discharge stroke. While a rotary-piston pump can enable single use / fully disposable filling, this requires the pump itself to be disposable, as the pump itself is a part of the wetted path. While such pumps do exist, in practice, rotary-piston pumps are generally made of re-usable materials and require cleaning and sterilization prior to use. Therefore, the risk of cross-contamination (for example, due to insufficient cleaning and/or sterilization) is higher for reusable rotary-piston pumps than for peristaltic pumps. Additionally, re-usable rotary-piston pumps are prone to damage, as the piston and cylinder have very tight dimensional tolerances to operate smoothly and without leakage. Finally, rotary-piston pumps may be unsuitable for drug products which are sensitive to shear stress. However, due to the high pressures achievable by rotary-piston pumps, they are preferred when the drug product has a high viscosity.
3. Time-pressure filling systems utilize an experimentally-determined correlation for volume dispensed as a function of pressure, and in some systems, as a function of temperature as well. This correlation varies by drug product. During filling operations, when the dosing valve is open, the high-speed control system integrates the curve of pressure vs time to calculate the volume dispensed. The dosing valve closes when the volume dispensed reaches the desired set-point. Time-pressure systems can be either single-use / disposable, or they can be reusable and require cleaning and sterilization prior to each use. Similar to rotary-piston pumps, the risk of cross-contamination (for example, due to insufficient cleaning and/or sterilization) is higher for reusable time-pressure systems than for peristaltic pumps.

With proper sizing and design, all three pump mechanisms can be made to operate at high-speed and with high accuracy and precision.

## Wetted Path

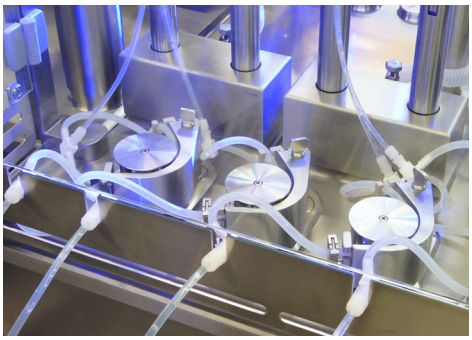
In addition to the pumping mechanism, the remainder of the wetted path should be considered. A sterilized single use / disposable wetted path carries less risk for cross contamination from one batch to another. A re-usable wetted path requires cleaning after each use and sterilization prior to the next use.

## Vacuum Filling

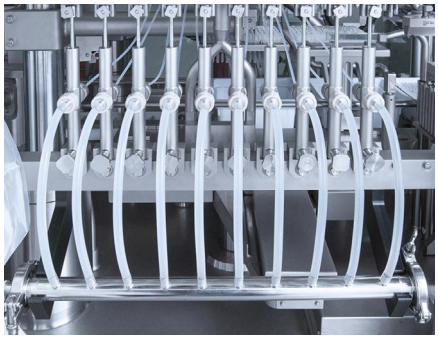
When filling syringes or cartridges, applying a vacuum to the container prior to and during the initial dispensing of drug product allows for the residual air bubble at the nozzle of the container to be minimized.

## Number of Dosing Stations

The number of dosing stations affects the maximum line speed or the overall throughput capability of the machine. A larger quantity of dosing stations increases the maximum line speed. Each dosing station may have its own individually-controlled pump, or all dosing stations may share a single pumping mechanism via a common filling manifold. If a single pump or pumping mechanism is shared by multiple filling nozzles (for example, as is the case for a time-pressure filling manifold with multiple dosing stations) then the drug product flow rate for each filling nozzle needs to be considered for each filling nozzle, and the time that each dosing valve is opened needs to be controlled individually.



*Four peristaltic pumps. Image courtesy of Optima Packaging Group GmbH. Used with permission.*



*Ten rotary piston pumps. Behind the array of pumps can be seen ready-to-use containers in nest and tub format. Image courtesy of Bausch+Ströbel. Used with permission.*

## Dosing Accuracy Verification

There are various approaches to evaluating the dosing accuracy:

1. 100% in-process [weight] check (IPC) enables the confirmation that each container has the specified volume of drug product, and if it doesn't, then that container gets automatically rejected. Because performing 100% IPC requires additional processing time, the line speed is effectively reduced compared to sampling-based IPC

2. Sampling-based IPC may be implemented to enable a faster line speed and when the purpose of the IPC is to correct minor performance drifts in the pumping mechanism over the course of the batch. Though, if a sampling-based IPC is utilized and there is an out-of-specification volume measurement, consider what will be the procedural response to such an event. Will only that container be rejected? Will all the containers filled between the last good measurement and the next good measurement be quarantined and evaluated further?

3. For cartridges which are introduced without a pre-installed seal / cap, sensor filling may be an option. With sensor filling, the plunger is inserted into the container first, prior to dispensing any drug product into the container, and using a servo-controlled plunger placement mechanism. Thereafter, the drug product is dispensed into the container through the nozzle of the container. A sensor monitors the nozzle, and the automated system stops the filling operation when the sensor detects that the container nozzle has been filled. Considering that the plunger placement process is servo-controlled, and the plunger placement location may also be confirmed by visual inspection, the sensor-filling operation can be performed without the need for additional IPC.

In the event of an underfilled container, some equipment may be able to perform an additional dispense to bring the dose to the appropriate level.

## Inert-Gas Purge Capability

For drug products which are sensitive to oxygen, the container headspace can be purged with nitrogen or other inert gas, as appropriate. There are various methods available for purging the headspace, which include:

1. Placing the filled open container near a nozzle which blows the inert gas into the container and displaces the air. Considering that the container is still within a laminar airflow of the RABS or isolator enclosure, there is a risk that the inert gas itself can be displaced by air, so it is important that the elastomeric closure be placed immediately after the inert gas purge has been completed. This method is generally applicable for vials, as the mechanics of plunger placement into a syringe or cartridge (for example, the plunger traveling through the plunger holding fixture or through a vent tube), will result in a displacement of the inert gas by air.
2. Encapsulating the container, or the full nest of containers, within a small chamber in which the air is purged via one or multiple vacuum pulses and replaced with inert gas. Thereafter, the elastomeric closure is placed. This method allows for precise control of the final gas concentration and pressure, and it eliminates the risk that the inert gas will be displaced by the airflow surrounding the container.

## Plunger Placement Capability

For syringes and cartridges, the choice of plunger placement method is determined by considering whether a residual bubble in the final container is tolerable, or whether a bubble-free container is required, as well as how much control over the final plunger position is required. The following plunger placement methods are generally available, with some variations of these methods across the various OEM offerings:

1. **Vacuum-only:** Prior to plunger insertion, a vacuum is applied to the syringe or cartridge barrel. The plunger is partially inserted in to barrel opening. Once the sealing rib of the plunger has been inserted into the barrel opening, any residual air will be sealed in the container. Thereafter the vacuum is released. Then the mechanism holding the plunger is released, and the differential pressure across the plunger (resulting in a downward force against the plunger) pushes the plunger into the barrel. As the plunger moves further into the barrel, the headspace volume will decrease, the pressure will increase, and the differential pressure across the plunger will also decrease. The plunger will keep moving until the frictional force overcomes the force due to the differential pressure across the plunger. The final plunger position may vary slightly from one container to another, as small dimensional differences between containers and plungers across the batch also affect the frictional forces. This method always results in a residual bubble, though the size of the residual bubble can be minimized to the extent possible and is highly dependent on the target fill volume in relation to the nominal fill volume defined by any respective container.
2. **Servo-controlled insertion rod with vacuum:** Prior to plunger insertion, a vacuum is applied to the syringe or cartridge barrel. The plunger, being held by a servo-controlled insertion rod, is partially inserted in to barrel opening. Once the sealing rib of the plunger has been inserted into the barrel opening, any residual air will be sealed in the container. Thereafter, the vacuum is released, though the mechanism holding the plunger to the insertion rod is maintained. The servo-controlled insertion rod pushes the plunger further into the barrel. As the plunger moves further into the barrel, the headspace volume will decrease, the pressure will increase, and the differential pressure across the plunger will decrease. The insertion rod stops moving when the desired plunger position has been reached. Thereafter, the mechanism holding the plunger to the insertion rod can be released. This plunger placement method always results in a residual bubble, though the size of the residual bubble can be minimized to the extent possible. In any case, the final plunger position will be determined by:
    - The container dimensions, which will nominally be the same for all containers of the specific container format chosen,
    - The volume of drug product dispensed into the container,
    - The vacuum pressure applied to the barrel, if any, prior to filling, and
    - The vacuum pressure applied to the barrel prior to insertion of the plunger

The final plunger placement position setting is chosen such that it results in a residual bubble which is at atmospheric pressure. By considering the volumes of the empty container, the drug product, the residual air bubble at the nozzle, the residual air volume when the sealing rib is inserted into the barrel, and then modeling the system under the ideal gas law, the final plunger placement position, which results in a residual air bubble at atmospheric pressure, can be calculated theoretically and then optimized empirically.

3. **Vent tube:** A vent tube is a tube with an outer diameter which is smaller than the inner diameter of the syringe or cartridge barrel. The vent tube is inserted into the barrel such that the tube opening is slightly above the drug product level. A plunger is inserted through the vent tube by a servo-controlled insertion rod. As the plunger travels through the vent tube, the air in front of the plunger is pushed downwards through the vent tube, exits the bottom opening of the vent tube, and then travels upwards and out of the barrel. Therefore, the barrel is "vented," hence the term "vent tube." The plunger exits the vent tub with the sealing rib just above the liquid level. The plunger expands and seals against the barrel. Thereafter, the vent tube is removed from the container. The vent tube process can also be used with the application of vacuum during the plunger insertion process, which enables achieving a bubble-free final container. One important consideration when choosing a vent tube is that, during the plunger insertion process, the plunger is compressed more by the vent tube than it would be if the plunger had been traveling through the barrel alone. Therefore, the compatibility of the vent tube with the plunger needs to be checked. Some plungers, especially those with coatings or laminations that extend through the plunger sealing rib or beyond, may be damaged by the combination of additional compression and frictional forces while traveling through the vent tube.

4. **Sensor filling:** for cartridges which are introduced without a pre-installed seal or cap, sensor filling may be an option. With sensor filling, the plunger is inserted into the container first, prior to dispensing any drug product into the container, and using a servo-controlled plunger placement mechanism. Thereafter, the drug product is dispensed into the container through the nozzle of the container. A sensor monitors the nozzle, and the automated system stops the filling operation when the sensor detects that the container nozzle has been filled. Afterwards, a septum and seal are applied to the cartridge nozzle, thereby sealing the cartridge. This method results in a bubble-free final container.

For any of the above plunger placement methods involving the application of vacuum, the air pressure between the sealing and stabilization ribs of the plunger must be considered. It is generally recommended that the application of vacuum be released once the first sealing rib has been inserted into the container and is fully seated within the internal barrel surface. This is so that the pressure between the ribs is ensured to be at atmospheric pressure. This helps mitigate the risks that are posed by a residual vacuum pressure, namely, the risk of pulling contaminants into this interstitial space, as well as the risk of drug product egress into the interstitial space.

Also, for any of the above plunger placement methods involving the application of vacuum, the purpose of the vacuum application is to minimize the size of the residual bubble. Therefore, it is important that the absolute pressure applied to the barrel be as low as possible (i.e., strongest possible vacuum) without causing the drug product to boil and without causing machinability problems with the mechanism which is holding the plunger during plunger placement. An exception to this is when a residual air bubble of a specific size is required for the purpose of aiding the agitation of the drug product prior to drug product administration.

## Number of Stopper/Plunger Placement Stations

The number of stopper/plunger placement stations affect the maximum line speed or the overall throughput capability of the machine. A larger quantity of stopper/plunger placement stations increases the maximum line speed.

## Electrostatic Reduction

Static electricity can pose challenges during fill/finish operations, including:

1. Attraction of particulates onto the surfaces of equipment or onto the surfaces of the containers or closures.
2. Causing containers to move out of their expected positions and or to adhere to parts of the equipment. This can result in machinability problems. Alternately, if this occurs during the weighing process, it can result in inaccurate weight measurement.
3. Causing drug product to creep or escape its final container, especially in powder filling applications.

Static can be mitigated by using static dissipating materials for equipment, as well as introducing static eliminating devices, such as de-ionization bars or blowers, as appropriate given the aseptic processing environment.

## Particulate Control and Monitoring

Controlling the generation, elimination, and prevention of particulates can involve a variety of methods, including:

1. Electrostatic reduction (as noted above).
2. Proper airflow profiles and speed. For example, downward unidirectional or laminar air flow, or in the case of lateral airflow, the flow is going from the cleanest / most critical zones to dirtier / less critical zones.
3. Separation of unit operations to prevent migration of particulates from particulate-generating operations. Separation of unit operations can include increasing the distance between unit operations, and/or placing physical barriers, such as glass walls, between unit operations.
4. In-process air sampling (continuous particle counting and microbial air monitoring with settle plate storage). Air sampling alarms can also be integrated into the fill/finish equipment for enabling automatic actions in the case of a high particulate alarm (for example, automatically stopping the filling activity and/or automatically rejecting product which was exposed during the high particulate event).

## Material Out-Flow

Consideration should be given to the out-flow of all materials, whether good product, rejected product, or waste. For example, if waste is generated in an isolator, it will not be possible to open the doors to the isolator to remove the waste. In this case, how will the waste be collected, and when the waste receptable is full, how will the waste be removed from the isolator? If the drug product is hazardous, how will the downstream manufacturing personnel be protected from exposure to contaminated surfaces of waste or to external surfaces of the final containers? Is a post-filling decontamination process required to be performed?

## In-line Inspection and Rejection

Ideally, there will be automatic in-line inspection for all containers processed, with automatic rejection for any containers which contain critical defects or for which the fill/finish unit operations did not complete successfully. Automation enables the inspection and rejection process to be performed in-line within the automated fill/finish manufacturing process, thereby offering the following benefits:

1. Eliminates the risk of variability associated with human inspection
2. Reduces the total personnel required to execute the manufacturing operations
3. Enables the automatic collection and reporting of data
4. Prevents the passing on of defects to downstream unit operations or the patients.

## Automation and Data Management

The considerations for automation and control systems, as well as data collection, management, and reporting, are numerous and deserve their own comprehensive review. For the purposes of this discussion, the following succinct points are offered:

1. All computerized components, with the potential to impact the successful execution of cGMP manufacturing operations, should be qualified and conform to applicable regulatory requirements and good data integrity practices.
2. Electronic parameterization of machine or process settings is preferrable to physically adjusted mechanical settings, as the digitization of such settings enables modification of such parameters via user-access controls and without the need to break-down equipment, automatic logging of modifications, auditing, automatic detection of an incorrect setting, and interlocking of the process execution.
3. While most equipment is delivered with stand-alone control systems and human-machine interfaces (HMIs), integration of all fill/finish equipment into a common Supervisory Control and Data Acquisition (SCADA) system is preferrable to stand-alone systems. The SCADA system enables remote monitoring, alarming, and troubleshooting, and integrates all equipment into a common data collection system, allowing for the automatic generation of comprehensive electronic reports for the full fill/finish process.
4. Electronic batch execution systems can be utilized to enable recipe management from a single location, migrate from paper batch records to electronic batch records, automate the checking of raw materials prior to batch use, and reduce the potential for documentation errors or quality oversights.
5. It is recommended that the applicable fill/finish OEM be engaged to incorporate the desired systems capabilities. Where the OEM is unable to provide a comprehensive solution, a control systems integrator can be engaged to work with the associated OEMs and deliver the desired functionality. Most OEMs will be protective of their intellectual property, such as control systems programs, and therefore may not wish to release some or all parts of the control system source code to the control systems integrator. It is important that the scopes of work for the applicable OEMs and the control systems integrator include the necessary collaboration to enable the desired higher level automation functionality.

As companies continue to focus on strategies to accelerate their path to market, manufacturing planning becomes a critical step in the path to commercialization. West's collaboration with OEMs for product and primary packaging development is critical to ensure that **West's products and primary packaging** can be handled and processed successfully by existing fill/finish manufacturing equipment. Ideally, the products and primary packaging can be processed by existing equipment with simple parameterization or process tuning, or potentially with a format part change-over, rather than requiring the fabrication of a new filling line or line addition. This can reduce the customer's time to manufacturing readiness, enabling a faster speed to market. Whether you chose to work with a CMO or build internally, you can **work with West** to identify container closures solutions and how they will work with your manufacturing processes.

---

To find out more about options and offerings available in support of selecting packaging components for your fill finish line, **Contact Us** so that we can connect you with an account manager in your region.

**West Pharmaceutical Services, Inc.**
530 Herman O. West Drive, Exton, PA 19341 USA
610.594.2900

www.westpharma.com



11720 0523