Sharp

Navigating the Fill Finish Process

A step-by-step guide to navigating the fill finish process

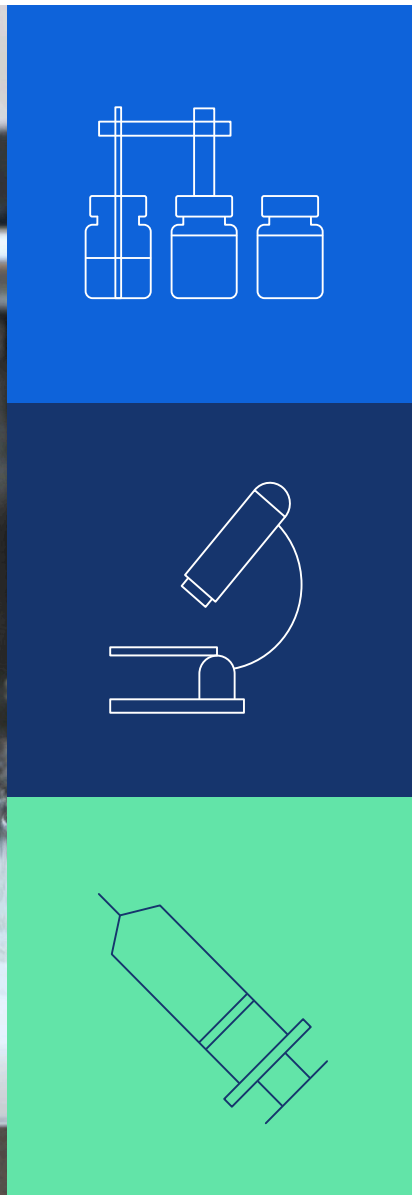
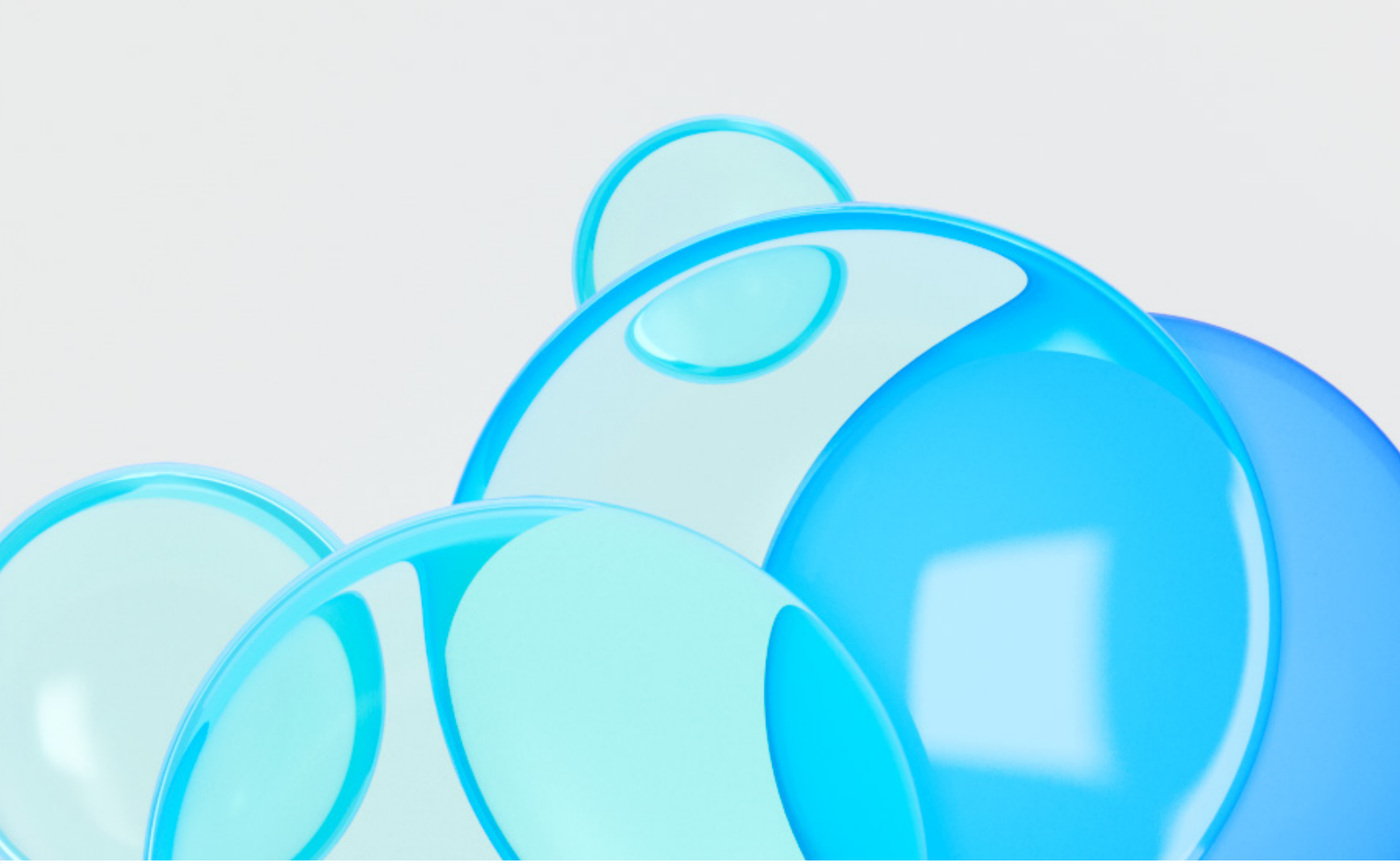


Table of Contents



Introduction

You're here, likely because you are seeking formulation, sterilization, and filling services for your drug. Our guide maps out the journey from onboarding to batch release and highlights facility differences between CMOs so you can understand the impact on your product quality and safety. So, let's get started!

What happens when you determine who your CMO will be and you are now ready to begin the work? There are three phases to your drug production:

Planning & preparation → Execution → Review & Release

Planning & Preparation

What's involved?

The planning and preparation phase includes all activities that occur before your drug product is pulled into the cleanroom to begin formulation activities.

Multiple Teams

- Kickoff

Process Engineering

- Formulation Development
- Lyo Cycle Development
- Technology transfer
- Batch Record (BR) Development
- BR Review & Issuance

Quality Control

- Method Development
- Method Transfer
- Method Qualification and/or Validation
- Release Testing

Materials

- Material Acquisition
- Material Specification Creation & Review
- Material Release Testing

Quality Assurance

- Review and release of all quality documents (BR, TM, PR, MSPEC, etc)

All Teams

- Engineering Run

Teams

→ Materials
→ Process Engineering
→ Manufacturing
→ Quality Control
→ Quality Assurance

The Kickoff Meeting

The project kick-off meeting serves as the introduction to your dedicated CDMO team. They will discuss tasks, share technical details, and give you the stage to share details about your drug product's significance. This sets the foundation for a successful collaboration, and it allows the CDMO to begin work.

Formulation Development

If applicable, formulation development is the first task that is performed. It is helpful to have the CDMO perform formulation development for your drug product, because the knowledge and technology will remain onsite for when the fill finish process is drafted. Formulation development can involve everything from selecting appropriate excipients to optimizing an already prepared process.

Studies in formulation development can include:

- Freeze-thaw testing
- Shear testing
- Filterability
- Syringeabililty studies
- Components compatibility
- Hold time studies

Lyophilization Development

For lyophilized drug products, it's critical to develop or optimize the lyophilization cycle. Some CDMOs provide this service, adapting the cycle to their specific lyophilizers for a seamless transfer. Lyophilizers vary in size and efficiency, which can affect cake quality if the cycle is not optimized. Look for a CDMO with a lab-scale lyophilizer for quick cycles and studies, ensuring readiness for transfer to larger industrial lyophilizers.

Planning & Preparation

Lyophilization development can include:

- Thermal characterization
- Solvent removal optimization
- Stability studies
- Process robustness and tech transfer

Technology Transfer

If you have an established formulation process, you will need to transfer that knowledge to the CDMO. The CDMO will replicate the process at their site to verify its feasibility and adherence to your set parameters. This verification is also applicable to terminal sterilization processes, such as steam sterilization, that will be conducted at the CDMO.

Batch Record Development

Once all critical processes and parameters for formulation, sterilization, and filling are determined, the batch record will be written. This is a document that contains step-by-step instructions and specifications for all activities related to your GMP production. Any operator, chemist, or other employee of the CDMO that is performing a task in the batch record will need to sign into the record and document each step they perform.

Batch Record Review & Issuance

After the process engineer drafts the batch record, it undergoes internal review by relevant groups (Validation, QC Microbiology, QC Analytical, Manufacturing: Formulation, Filling, Component Prep) and the sponsor. Comments are provided by each team and the sponsor, andthe author incorporates them into the updated batch record. The finalized document then goes through a final review process, starting with the client and then circulating among the internal groups mentioned earlier, ending with QA. Upon QA approval, a physical copy of the batch record is issued a few days before production begins.

Method Development

Your CDMO may offer method development. This is exceptionally helpful if you are developing your formulation at the CDMO, because method development can occur simultaneously with formulation development activities, saving you time in your development. Method development will also be useful to sponsors that have a method established but require optimization.

Planning & Preparation

Method Transfer

If a working method has already been established, but needs to be transferred to the CDMO, then a method transfer can be performed. The CDMO will replicate the method at their site, by performing feasibility runs, to confirm it is a working method that meets set criteria by the sponsor. Method transfers are not needed if development is performed onsite.

Method Qualification/Validation

Once a method is established at CDMO (either newly developed or transferred) the CDMO will need to qualify the method to demonstrate it is suitable for routine testing.

The qualification will include specificity, accuracy, precision, linearity, limit of quantitation, and limit of detection.

Method validations are performed before a drug product goes commercial to demonstrate the method's robustness, and it will include all of the tests in the qualification in addition to robustness (testing with varied parameters to evaluate performance).

The validation should demonstrate that the method is stable even with parameter variations during testing.

Material Acquisition

All materials and chemicals for your GMP fill will need to be ordered and sourced.

Material Specification Creation & Review

Material specifications will need to be created for any unique chemicals or materials (e.g. your API, a new excipient, or a unique container or tubing). These serve as a documented review of any incoming materials or chemicals to confirm that the sourced material is the correct item and it adheres to the standards set forth in its Certificate of Analysis. New materials will undergo in-depth quality testing until three consecutive lots are reviewed and released, at which point the extent of the quality testing can be relaxed.

The materials group at the CDMO will write the material specifications for any new materials, and quality assurance will review the documents to be released.

Planning & Preparation

Material Release Testing

All materials and chemicals will undergo release testing as described in the items' material specifications. Any consumable material or chemical used in a GMP production must be tested and released before it can be used.

The materials group will perform these tests, with help from the analytical lab to perform chemical release tests. Once the products are released, the materials group will load all materials, as listed in the batch record, into a locked cage that will move to the cleanroom to begin activities.

Quality Assurance Review & Release

Quality assurance will review all quality documents that are prepared for a GMP production. These include batch records (BR), test methods (TM), protocols (PR), Material Specifications (MSPEC), among other documents.

Engineering Run

The engineering run is the last step before performing the first GMP fill for a new fill finish project. This is essentially a mock GMP-run that follows the written batch record, with a few caveats; sterile filling activities may be reduced and this run is typically non-sterile. This process serves multiple critical functions:

1. The engineering run tests the full production process and identifies any critical process updates or parameter changes that need to be implemented before starting a GMP run.

2. The engineering run serves as critical, hands-on training for all employees involved in the production.

3. And finally, the engineering run validates the GMP process. This ultimately protects the patient, as the quality of the process is tested and optimized before it is used to produce drug product for patients.

Once all of the applicable activities listed above are complete, the CDMO will be ready to begin your GMP drug product production.

Execution

What's involved?

The execution phase includes all GMP activities that occur during your drug production, including formulation, filtration, aseptic filling, visual inspection, and all associate in-process testing or quality oversight.

Manufacturing

- Batch Formulation
- Sterile Filtration
- Aseptic Filling
- Terminal Sterilization
- Visual Inspection

Quality Control

- In-Process Testing

Quality Assurance

- On-the-floor quality oversight

Teams

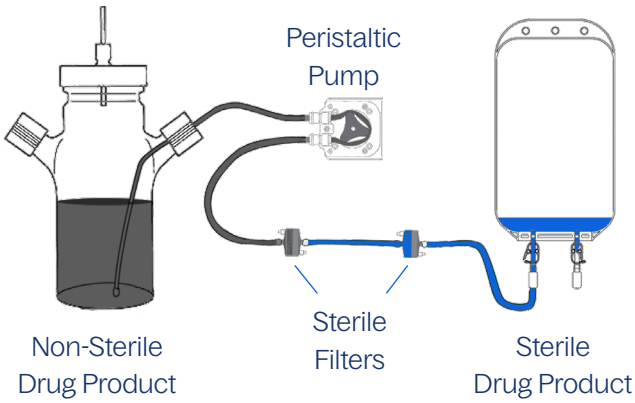
→ Manufacturing
→ Quality Control
→ Quality Assurance

Batch Formulation

The drug product is formulated in a Class C (ISO Class 10,000) cleanroom. All materials used in the process will have been sterilized to ensure bioburden which can clog the sterile filter, remains low. Each formulation process is unique. Some may require thawing overnight in a temperature-controlled unit, special handling, dedicated technology, or unique mixing processes. This process will be explicitly written in step-by-step directions that the formulation associate will perform and document. All steps require verification from a second party, which will most be a second formulation associate that assists with the formulation.

Sterile Filtration

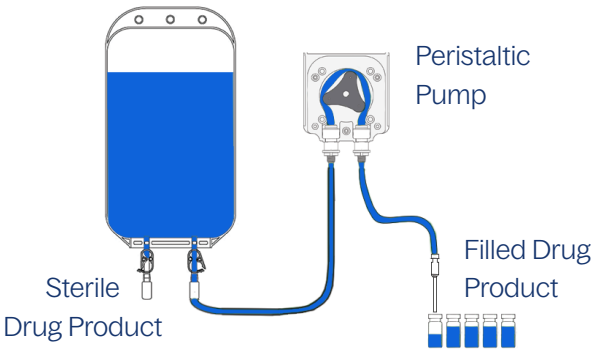
Once the drug product solution is formulated, the vessel containing the drug product is connected to a second, sterile vessel via tubing with two sterile filters attached in between. The drug product is gently pumped through the tubing via a peristaltic pump and filtered through the redundant filters. The first sterile filter is considered the "bioburden reduction" filter and the second is the "sterilizing filter".



The bulk drug product is typically collected into either a glass mixing vessel or a bioprocess bag. This container will have a sterile connection to attach the drug product to the filling line, and a connection to a sterile filter that allows air to flow out of the bag or vessel as it is filled, without compromising the sterility of the drug product.

Once sterile filtration is complete, the sterile filters will undergo post-use integrity testing to confirm the filters are intact and unbroken.

Execution



Aseptic Filling

If the sterile filters pass integrity testing, then the drug product solution is connected to a filling line to begin aseptic filling. For the greatest sterility assurance level possible, drug product should be filled in a sealed and sanitized Grade A (Class 100) space. Isolators are the most effective tool to mitigating contamination risk in aseptic filling.

The drug product solution will remain outside of the isolator-based filling line and will be connected to the fill line assembly in the isolator via an aseptic connection through the wall of the isolator. The drug product will be drawn through the fill line assembly and a "purge" sample will be collected to ensure all air is out of the filling line before starting.

The CDMO will begin filling units one at a time and taking weight checks. Once three consecutive and passing weight checks are achieved, filling can begin. The drug product will be filled into your container closure system while inside the isolator. All tools and materials used in the fill will have been sterilized and aseptically transferred into the isolator. Every 50-150 filled units, a weight check will be performed to confirm that the fill volumes are accurate.

Terminal Sterilization

If your injectable drug product can withstand terminal sterilization, then it must be sterilized in this way. If this is applicable to your project, then you may skip the sterile filtration step, however the filling line must still be prepared as it is for aseptic fills. So, this would still require a vapor hydrogen peroxide sanitization cycle prior to filling (if using an isolator-based filling line).

There are multiple methods of terminally sterilizing drug product, including steam-sterilization in an autoclave, gamma-radiation, and electron beam (e-beam) irradiation among others. Terminal sterilization is performed after drug product has been filled into its final container.

Execution

Visual Inspection

After the drug product has been filled, 100% of the lotwill be visually inspected for minor, major, and critical rejects. An Acceptable Quality Level (AQL) inspection will be performed to confirm the reject rate.

Each reject category – minor, major, and critical – will have a limit of allowed rejects, with minor rejects having the highest limit and critical having the lowest limit. If the reject limit is met for any category, then the lot cannot be released. Otherwise, the lot will have passed visual inspection and the drug product will be moved to a temperature-controlled unit (TCU) where the product will remain until all testing and review has been completed.

In-Process Testing

During the formulation process, in-process analytical testing may be required. For example, if a concentration assay is needed, then a sample of the drug product formulation will be pulled from the formulation and handed over to the onsite analytical lab to perform testing.

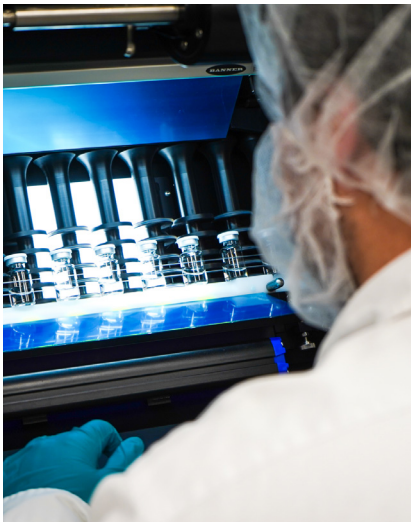
There are two types of tests: in-process or in-process STAT testing. In-process tests use samples pulled during formulation, but formulation continues once the sample is pulled. In-process STAT testing requires the formulation remain on hold until results come back.

The objective of STAT testing is to rectify the drug product formulation based on the test results obtained. General in-process tests serve to provide substantiation that the production process (including filtration and filling) has not adversely impacted the drug product solution.

On-the-floor Quality Oversight

Some CDMOs will offer on-the-floor quality assurance. This is where quality assurance employs a team member to remain in the room during production activities to ensure operators are following the batch record, and to provide support in the event of an unplanned deviation. The purpose of having quality personnel in the production room is to reduce errors and cut down on deviations.

Certain CDMOs provide the added benefit of on-the-floor quality assurance, whereby a dedicated team member is present in the production area during GMP manufacturing activities. This proactive approach ensures that operators adhere to the batch record guidelines and offers immediate support in case of unplanned deviations. By having quality personnel on-site during production, errors and deviations are minimized, thereby promoting a streamlined and quality-centered manufacturing process.



Review & Release

What's involved?

The review and release phase includes all activities that occur after your drug product is filled. Here is what it involves:

Quality Control

- Release Testing

Quality Assurance

- Review and release of all completed quality documents (batch record and completed test methods)

Teams

→ Quality Control
→ Quality Assurance

Release Testing

After drug product has been filled, samples will be pulled from the batch to complete release testing. This may include quality testing, such as concentration, pH, appearance, impurities, among others.

Microbial testing will also take place, including bioburden, endotoxin, and sterility. If your CDMO has the capability to do this testing in-house, they will likely require that this is completed at the CDMO. Incubated samples require two weeks of incubation, so all QCM testing will require a minimum of three weeks to complete.

Review and Release

The last step involves conducting a thorough quality review of all completed GMP records, including the batch record and any test methods performed for in-process and release testing.

Quality assurance will collaborate with each team to address and close out any deviations that may have occurred. Once all the necessary work is completed, the documents will receive a final review by quality assurance. If the work meets the quality standards, quality assurance will initiate a release of the batch.

CDMO Comparison

Choosing a CDMO for filll finish is challenging due to various factors beyond facilities, such as communication, expertise, and regulatory support. However, the facility where your drug product is manufactured is vital for sterility assurance, flexibility, and scalability. This section will outline the differences in facilities and equipment and their impact on your drug production.

What's Discussed:

Has the greatest impact on sterility assurance

Filling Environments

- BSC Hood
- Open Cleanroom
- Open RABS
- Closed RABS
- Isolator

The big debate

Isolator Comparison

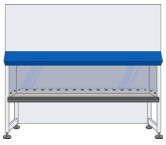
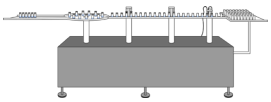
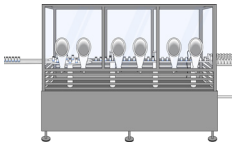
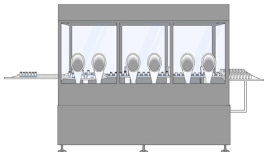
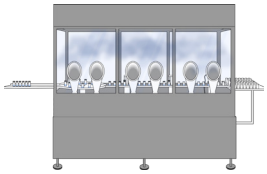
- Traditional Isolators (Glove-equipped)
- Gloveless Isolators (Automated workcells)

Has the greatest impact on scalability

Filling Equipment

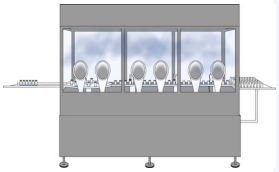
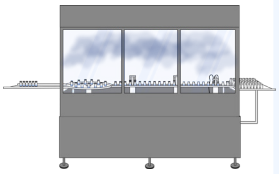
- Dedicated In-line Filler
- Flexible XY Filler
- Manual Filling
- Low Loss Fill Process

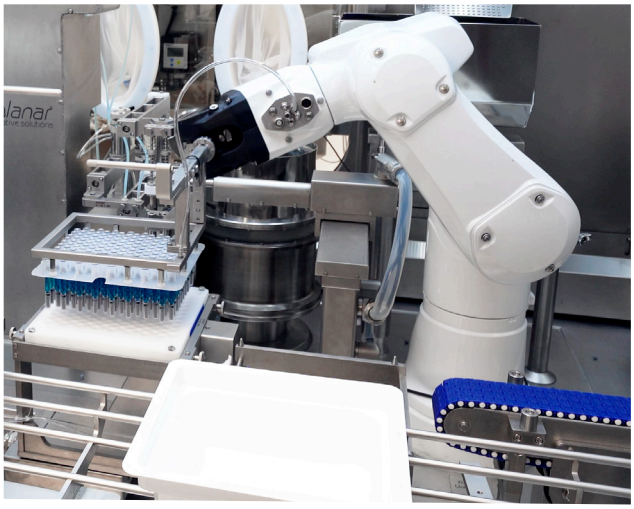
Comparing Filling Environments

Environment	Description	PRO	CON	Sterility Assurance
BSC Hood 	A semi-closed cabinet with airflow protection to maintain sterility. Typically placed in a Grade B cleanroom. Sterile gowning is required.	Efficient movement and flexible Easy equipment installation & maintenance	High risk of contamination due to limited physical barriers & lower cleanliness of surrounding area	TERRIBLE
Open Cleanroom 	An open environment featuring unrestricted airflow and limited barriers or partitions in a Grade A cleanroom. Sterile gowning is required.	Efficient movement and flexible Easy equipment installation & maintenance	High risk of contamination due to limited physical barriers	TERRIBLE
Open RABS 	A semi-closed system that provides a physical barrier between operators and the sterile product in a Grade A cleanroom. Sterile gowning is required.	Provides physical barrier between operator and sterile product	Still carries high risk of contamination compared to enclosed systems	BAD
Closed RABS 	An enclosed and sealed system designed to provide a high level of sterility assurance in a Grade B cleanroom. Sterile gowning is required.	Reduced risk of contamination with a closed and sealed space	Limited access & less flexible Maintenance & cleaning are more challenging	GOOD
Isolator 	An enclosed, highly controlled system with the capability to run sanitization cycles to enhance sterility assurance in a Grade C or D cleanroom. Sterile gowning is not required.	Provides the highest level of sterility assurance Minimal contamination risk	Higher investment & maintanence costs Can be less flexible	EXCELLENT

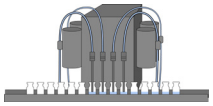
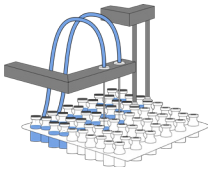
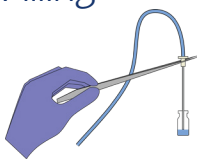
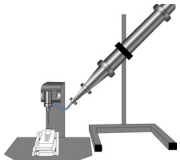
Isolators: Gloves or no gloves?

Some CDMOs offer gloveless automated workcells for drug product production to enhance sterility assurance by eliminating manual interventions. However, the absence of gloves poses a risk of premature fill termination and prevents error correction and unplanned deviations.

Environment	Description	PRO	CON
Traditional Isolators 	An isolator-based filling line with glove ports on the walls of the isolator allow operators to perform interventions or processing actions inside the Grade A space	Allows manual interventions during a fill if needed Excellent sterility assurance	Marginally inferior sterility assurance compared to gloveless isolators
Gloveless Isolators 	An isolator-based filling line without gloves is designed to fill product automatically. The operator will feed containers into one end and finished drug product will exit on the other side.	Increased sterility assurance by eliminating operator interactions during processing	Eliminates the ability to perform manual interventions, including necessary interventions for unplanned deviations



Comparing Filling Environments

Filling Equipment	Description	PRO	CON	Better for
Dedicated In-line filler 	A filler that is built to fill only one container type in a line, typically off a conveyor belt.	▲ Fast filling ▲ High repeatability ▲ Typically offers higher quality processing results	▼ Inflexible - can only fill one container type ▼ Typically has greater drug product loss (greater line loss)	High volume drug product fills
Flexible XY Filler 	A filler that must be loaded with containers in an XY-format. Typically these fillers can fill multiple container types and sizes.	▲ Flexible (able to fill multiple container types and sizes) ▲ Easier to adjust and optimize for each container type and presentation	▼ Slower filling ▼ Less repeatability & consistency than in-line fillers	Low volume drug product fills
Manual Filling 	Hand filling by holding a fill needle over the container. Single unit capping or plungering tools may be employed.	▲ Flexible (able to fill multiple container types and sizes) ▲ Limited drug product loss ▲ Able to fill very low volumes of drug product	▼ Higher contamination risks with manual processes ▼ Less repeatability and consistency than other processes	Extremely low volume drug product fills (e.g. Preclinical or Phase 1 studies)
Low Loss Filler 	A fill process currently only offered at BSM to reduce drug product loss. Product is dispensed one unit at a time.	▲ Very limited drug product loss (<10mL) ▲ High repeatability ▲ Excellent for shear sensitive drug product ▲ Excellent for viscous drug product	▼ Higher contamination risks with manual processes ▼ Less repeatability & consistency than other processes	Extremely low volume drug product fills (e.g. Preclinical or Phase 1 studies)

What's the verdict?

Opt for isolators

Isolator technology offers the greatest sterility assurance for injectable drug products, and regulatory agencies are pushing for drug products to be manufactured in this environment.

CDMOs that utilize isolators demonstrate a commitment to implementing cutting-edge technology for enhancing the quality of the drug products they fill.When choosing a CDMO, prioritize those thatoperate within isolators.

Go for gloves

Gloveless isolators are sometimes advertised as offering the best sterility assurance. However, glove ports pose minimal risk, and they allow easy access to the filling line and equipment for manual interventions if things go array during a fill.

If sterility assurance is large concern, opt for an automated filling process in glove-equipped isolators. The gloves act as a final recourse, allowingcritical corrections to sustain the fill process when necessary.

Fit the filler to the project

Your project requirements will help you determine what is the best filler to fill your product on.

If you require a small number of units for preclinical or phase 1 studies (<2K units), manual filling will work well for your needs.

If you need greater sterility assurance, repeatability, and reduced drug product loss, then the low loss fill process will be better.

For small batch needs (1K - 100K units), an XY filler grants flexibility, along with enhanced sterility assurance, precision, and repeatability.

For large-scale fills (100K+ units), an inline filler provides the speed needed with exceptional repeatability.

Quick Start Guide

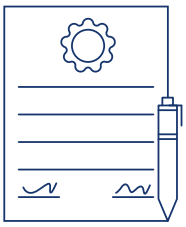
Ready to start your fill finish project at BSM? Review our Quick-Start Guide to understand the process from intro call to kickoff!

1

Introduction Call
When you first contact us, a sales representative will schedule an introduction call to learn more about your project and discuss SSM's capabilities.

2

CDA
Our CDA template will be shared for review and signature or we can review yours.



3

Product Survey
We will share a link to fill out an online product survey to gather information about your project requirements which will be used to put together a comprehensive quote. Alternatively, you may share an RFP.

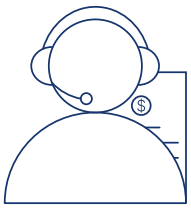
4

Quote & Timing
The completed product survey will be shared with your sales representative, and they will prepare a complete and accurate quote. Additionally, our current fill date availability will be shared.

Quick Start Guide

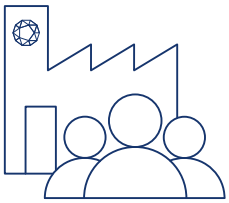
5

Quote Review Call
The quote will be shared with you, and your sales representative will schedule a follow up call to review it and answer any outstanding questions.



6

Site Visit at SSM
We encourage you to visit SSM for a facility tour. During the visit, you will have the opportunity to sit down with the SSM executive team over lunch to discuss the technical details of your project.

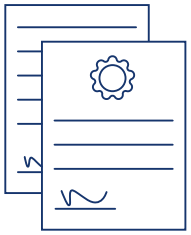


7

QA Audit
With every signed quote, a QA audit is included. Our team will work with you to schedule an audit date. Both on-site or virtual audits are offered.

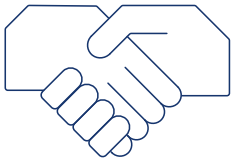
8

Signed Proposal & PO
Signing the proposal and PO is the final step before your project is started! Once these documents are received by your sales representative, a kickoff call will be scheduled.



9

Project Kickoff
The work begins! All SSM team members that will be working with you over the course of your program will join the project kickoff call to discuss the details of your project and obtain any necessary information to start work.



Contact us at info@sharpsterile.com to get started!

Sharp

About Sharp

Sharp Sterile (formerly Berkshire Sterile Manufacturing) provides sterile manufacturing services with the highest level of sterility assurance and quality achievable through the use of the most modern technologies for sterile manufacturing, stringent quality standards and highly trained employees. Sharp Sterile also provides ancillary support to their clients' drug productions such as analytical method development and validation, stability studies and formulation scale up.

Engineered to deliver

Contact Sharp

To learn more about how Sharp can support your fill finish project, contact the company here.

If you have any general questions, do get in touch at info@sharpsterile.com

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