Pii

A Complete Guide to Aseptic Manufacturing

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Introduction: Aseptic Manufacturing

“Researchers and drug innovators rely on processes like aseptic manufacturing to ensure that their parenterally administered therapies and biologics are safe and of high quality for the patients who need them.

Aseptic manufacturing is a uniquely challenging process that requires expertise and careful planning for successful execution. It is for this reason Pharmaceuticals International, Inc (Pii) has created this e-book—to provide valuable insights and guidance on aseptic manufacturing, sterile fill-finish, and its supporting activities.”

— Kurt Nielsen, Ph.D., President & CEO.

Aseptic Fill-Finish 101

Drug therapies can be introduced into the body orally, topically, by inhalation, or parenterally. Parenteral administration technically means non-oral administration, but it typically refers to the injection of drugs into the body intravenously, intramuscularly, or subcutaneously.

Parenteral drug delivery bypasses the body's natural defenses against bacteria and viruses, which increases the risk of infection to patients. Consequently, parenteral drug products and biologics must undergo sterilization to destroy any potential contaminants and ensure patient safety.

There are two ways a sterile drug product can be manufactured:

Terminal Sterilization

Terminal sterilization is conducted after a drug has been manufactured and involves the use of heat, radiation, and/or filtration. However, this is not always feasible and can negatively affect the product and its container. As formulations become more complex, the number of drugs that become less effective when exposed to heat or radiation and cannot be terminally sterilized grows.

Aseptic Fill-Finish

This is a process where the drug product, container, and container closure are first sterilized separately and then brought together. Combining the product, container, and closure is done in a cleanroom and often uses special equipment that is self-contained in a sterile environment. The aseptic fill-finish process is challenging and complex, and it is usually chosen when terminal sterilization is not suitable. The terms 'aseptic fill-finish' and 'sterile fill-finish' are often used interchangeably.

Sterile Manufacturing Process

Sterile fill-finish involves harmonization and complex interactions between specialized personnel, sterilized drug products, fill-finish equipment, containers, cleanroom, support components, and sterilized filling components.

Bulk Drug Sterilization
The drug or biologic must be sterilized before the filling process, typically done by filtration.

1

Component Sterilization
All equipment, components, and containers are sterilized. Sterilization is achieved with steam autoclaves, dry heat ovens, radiation technology, and clean room airlocks.

2

Aseptic Filling
Sterilized containers are transferred to the filling machines, filled with sterilized drugs, and then stoppered and sealed with a closure system.

***Terminal Sterilization**
Terminal sterilization is the process of sterilizing a drug product with moist heat after the formulation and filling process. It involves placing the final primary container into an autoclave.

Lyophilization
Unstable drug formulations are freeze-dried for stability before final closure. To do this, filled and partially stoppered vials and glass are transferred from the filling machines to the lyophilizer.

*Not all drugs require Terminal Sterilization or Lyophilization

Parenteral Container Packaging Systems

Choosing the correct container is crucial for the stability of the drug and the safety of the patient. Types of container systems include: RTS (Ready to Sterilize) and RTU (Ready to Use, also known as pre-sterilized).

Some examples of vials, prefilled syringes, and cartridges used during the aseptic manufacturing process include:

Glass
Borosilicate Glass for its excellent barrier properties, chemical resistance, regulatory acceptance, and a broad range of applications served.

Image courteous West Pharmaceuticals

Polymeric
Polymeric materials such as cyclic olefin copolymer (COC). This combines glass and COC for greater formability, break resistance, lightweight, glass-like transparency, strong barrier, and chemical compatibility. These systems are ideal for high-value, complex molecules.
- Crystal Zenith® CZ system

Hybrid
A hybrid material consisting of a molded, engineered polymer and an inert glass-like barrier coating system. The inert glass-like barrier is chemically resistant, contaminant-free, and consistent surface irrespective of the container geometry or materials of construction.
- Si02® system

Challenges Faced in Aseptic Fill-Finish Processes

Aseptic manufacturing of parenteral drugs is fraught with many challenges— with the growing diversity in drug product composition exacerbating some of them. From start to end, sterile fill-finish requires deliberate planning, skilled technical personnel and project managers, and specialized and modern equipment and facilities.

Here are some challenges commonly faced during sterile fill-finish projects:

Maintaining product stability:
Many biopharmaceuticals are volatile or sensitive, and their structure, potency, and stability can be altered during processing and filling. Extra care must be taken, especially during stages involving significant temperature changes, to maintain the drug product's stability.

Maintaining personnel sterility:
Specialized personnel are essential for the sterile fill-finish process, but they present the most significant risk of contamination to the drug product. The use of robots to automate aseptic processing can help reduce the number of personnel needed in the cleanroom (and consequently the risk of contamination). Still, it cannot completely eliminate the need for them.

Conducting effective inspections:
Drugs and biologics vary in appearance and viscosity and are packaged in containers that also vary in transparency, color, and thickness — all of which can make visual inspection challenging. More, the non-uniformity associated with manual inspection (which is often the chosen method) impacts the effectiveness and pace of inspections.

TECH TRANSFER

For Aseptic Fill-Finish

Tech transfer in pharmaceutical manufacturing operations.

Technology transfer is the transfer of drug product and process knowledge between development and manufacturing sites or between two manufacturing sites or organizations to achieve product realization.

No two tech transfers are identical, and sterile fill-finish projects have complex and unique features.

Parenteral Drug or Biologic Tech Transfer

Why is it done?

Moving the parenteral drug or biologic production to a new facility is a major decision driven by specific underlying conditions. Knowing why the transfer is being initiated can quickly steer the receiving facility staff to a start-point for the project, help reduce or eliminate unnecessary work, and shorten the time it takes to begin production.

Occasionally, a transfer might be initiated because of a quality issue at the current manufacturing site that cannot be resolved or a need for a secondary contract development and manufacturing organization (CDMO) because the current manufacturer is overbooked. Transfers with existing quality issues are more complex, and the urgent need for a secondary CDMO can create a lot of pressure.

Commercial strategies can also drive the need for a tech transfer. Some drug sponsors prefer to keep their development work in-house and outsource the initial drug production to a smaller specialty CDMO. And when appropriate, they move scaled-up production to another CDMO with capabilities suited for larger batch sizes.

Some drug production can be triggered by models predicting seasonal illnesses, driving the need to increase manufacturing rapidly. If the models miscalculate the peaks, drug production is pursued with even greater urgency.

Finally, the pharmaceutical industry as a whole is currently taking a close look at supply chain reliability— driven by gaps revealed by the pandemic. As pharmaceutical companies take steps to reduce risk, they are seeking new CDMO production facilities, ingredient providers, equipment manufacturers, and contract packagers, and are more closely considering the location of patient populations. In this case, the tech transfer is part of a larger supply chain transformation.

Significant Variations in Tech Transfers

While moving drug production to a new facility can occur for only a handful of reasons, analytical methods and manufacturing processes can vary greatly.

Transferring small clinical trial-batch operations

During the transfer of a small clinical trial-batch operation, particular attention may be paid to analytical methods, the drug product, and scalability testing. The formulation should have been tested for stability and quality for larger commercial-batch production. If not, the tech transfer must include this testing. And if it was properly tested, the records may reveal a problem that could be preempted before production begins, saving valuable time and resources.

Transferring commercial manufacturing operations

When transferring commercial manufacturing, more attention will be paid to understanding the current production process. Are all critical quality attributes known? How are they being addressed by the already validated process? Have any irregularities been recorded? Has the facility been inspected by a regulatory body, and what were the results?

If the transfer is due to an unresolved quality issue at another CDMO, understanding the process can be challenging. The gaining facility must conduct a root cause analysis as part of the tech transfer. The gaining facility must also be prepared to perform the arduous task of re-designing the process and building quality into the validation process.

Drugs Personas

Like tech transfers, no two drug products or biologics are the same, and drug innovation is being introduced at an extremely fast pace. Drugs can be complex, with the underlying sciences varying significantly. Individual drugs require different manufacturing processes, specific equipment, and special operator skills.

Injection is the most common delivery method for parenteral drugs and biologics. Therefore, the primary packaging could be a vial, ampoule, prefilled syringe, or auto-injector.

Parenteral drugs often require special temperature control in the manufacturing facility as well as the distribution supply chain. For many, temperature is a critical quality determinant. Temperature changes place the drug product's quality at risk, and real-time monitoring is required for drugs like this. Consequently, the receiving CDMO in a tech transfer must have adequate cold-storage space.

Some drugs are also highly potent and require special handling procedures to protect operators. They must be manufactured in an aseptic environment under strict containment conditions to prevent cross-contamination.

Transferring parenteral drug manufacturing to a new facility is an important decision, and before production can begin, a technology transfer must be conducted. Not all tech transfers are alike, but all can be done well by following some foundational best practices.

• The receiving facility needs to determine why the drug manufacturing is being transferred to a new facility and acquire a good start-point for the project.

• There should be no limits when gaining an understanding of the analytical methods and the current manufacturing process. Current quality systems should be compared with the receiving facility's quality systems, gaps should be identified, and quality improvement targeted.

• Understanding the drug persona is a critical component of a tech transfer as no two drugs are identical.

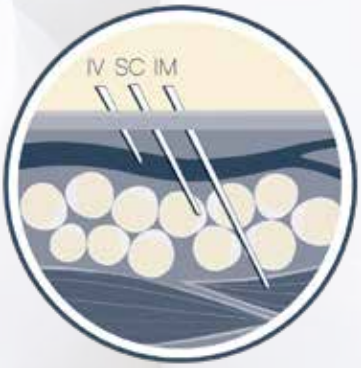
Applying these best practices will save significant time and resources, shorten the time to production, and deliver better results for the drug sponsor and patients.

Clinical Trial Manufacturing

Clinical trial manufacturing (CTM) of parenteral drugs is intended to produce batches that will support specific clinical trials.

CTM projects inherently contain many variables, must be synchronized with the start of a clinical study, and have specific packaging and labeling requirements, in addition to all the other standard Current Good Manufacturing Practice (cGMP) manufacturing requirements. Any delays or an inability on the part of the manufacturer of clinical trial supply can be particularly detrimental to the successful outcome of a clinical trial. It is advisable to start planning for clinical trial manufacturing as far back as a year before the trials start.

The acronym CTM is also sometimes used to refer to Clinical Trial Material(s). When clinical trials are about to commence, the development and supply of injectable products (IV, SC, and IM) and formulations are important. Some of these products and formulations include:



Solutions
- Aqueous, Nonaqueous, and Highly Viscous
- Inclusion Complexes
- Dispersed Systems
- Emulsions

Suspensions (Aqueous and Nonaqueous)
- Micelles
- Liposomes
- Polymeric Particles

Lyophilized Powders
A CDMO partner for clinical trial manufacturing should possess fill-finish machines specifically designed to handle small trial batch sizes. The CDMO should also provide services such as raw material characterization and sourcing, formulation development, manufacturing scale-up, pilot batch manufacturing, analytical method development and validation, active pharmaceutical ingredient (API) and excipient release testing stability testing, and packaging analysis. Finally, they should offer validated temperature storage of clinical trial materials.

Analytical R&D Support Sterile Fill-Finish

Sterile fill-finish is considered among the most critical steps in the parenteral production process— ensuring patient safety, pharmacological efficacy, and product quality. Parenteral drug product development and subsequent production rely on several integrated process elements operating in a systematic and coordinated environment.

Without a doubt, analytical support is one of the key process elements, as it is required at all stages of the product's life cycle, from early development to commercialization.

Any successful sterile fill-finish program starts with analytical services, more specifically with Analytical Research & Development (AR&D). AR&D groups are responsible for developing and validating analytical methods that are accurate, precise, reliable, and suitable for their intended purpose.

Objectives of Analytical Research & Development (AR&D)

Analytical methods are intended to establish the identity, purity, physical characteristics, and potency of drugs. Therefore, the methods are essentially designed to assist formulation scientists in gaining detailed process knowledge. This results in process optimization and the ability to transition from small scale to large commercial scale. Timely access to accurate analytical information is fundamental for formulation development work. Extensive interactions between analytical and formulation scientists are necessary to ensure analytical methods address the specific needs of each development project.

Another objective of AR&D groups is to develop methods robust and reproducible enough to be transferred to quality control (QC) laboratories. AR&D teams are counted upon to lead these transitional activities and guide QC teams in the process. Given the variety and complexity of today's drug therapies and delivery systems, AR&D scientific teams must be able to perform method development for a range of sterile fill-finish projects, such as suspensions, solutions, and lyophilized products in vials, cartridges, and prefilled syringes.

The pharmaceutical industry is constantly evolving, and the number of investigated compounds continues to increase. This leads to a higher demand for the development of new analytical methods. Every project is unique, and AR&D scientists in CDMOs must meticulously evaluate each project to determine if there is enough information for a successful tech transfer or if new methodologies need to be developed, all the while adhering to the customer's project timeline. AR&D teams also need to demonstrate that the analytical method is scientifically sound, fit for purpose, and can be easily adapted.

Instruments Required

Overcoming challenges associated with sterile fill/finish projects, scientists must be equipped with leading-edge instrumentation in the analytical R&D lab. The specific instruments required for the testing of injectable formulations include:

Break-loose and glide force:
The Instron Syringe Test Fixture accommodates a variety of syringe sizes to determine the breakaway force and glide force. Breakaway force represents the force required to start the syringe's fluid ejection, and glide force is the average force required to maintain an even flow of fluid out of the syringe. This equipment is essential for an AR&D lab serving drug developers to advance injectable therapies to patients.

Dissolution testing:
Described in the United States Pharmacopeia (USP) as Sotax Apparatus 4, dissolution and drug release testing using a flow-through cell is proven to characterize the active drug release in terms of bioequivalence and in vitro/in vivo correlation (IVIVC) in clinical studies and daily QC routines alike. AR&D teams with this capability can effectively support extended-release injectables.

Particle size analysis:
Accurate, robust, and reliable data is a must for informed decision-making related to certain types of formulations such as injectable suspensions, oral suspensions, and soft gelatin capsules. A laser diffraction particle size analyzer, like the Malvern Analytical Mastersizer 3000®, is versatile, compact, and ideal for the demanding workflows of CDMOs.

Nanoparticle, colloid, and biomolecular particle sizing, and particle charge measurements:
Accurately and easily characterizing particles in solutions is another essential capability for AR&D labs. Analyzing particle mobility and charge (Zeta potential) using Electrophoretic Light Scattering (ELS) and the molecular weight of particles in solution using Static Light Scattering (SLS) helps define drug product performance and manufacturability and generates vital information that the QC lab will use. An example of an instrument ideal for the accuracy required for complex parenteral drugs is the Malvern Analytical Zetasizer®.

Project Management

Project managers are assigned for the lifecycle of a sterile fill-finish project and serve as agents for the client with complete transparency. The project manager needs to fully understand the client's programs and their desired outcomes.

Project Managers are responsible for:
- Project continuity
- Client advocacy
- Collaboration across functional areas
- Strategy development
- Smooth, bi-directional CDMO- client communication

A great project manager will have the visibility of a senior decision maker; anticipate FDA needs, supply chain, technology challenges, and plan accordingly for success.

What Great Project Management Looks Like

Client advocacy
Project managers should serve as agents for the client. They must take the time to understand the project from the client's perspective fully and should understand the negative impact of not meeting timelines. For example, missing a critical timeline milestone will lead to the loss of 50% of the client's expected funding. Understanding how distinctive aspects of the project may negatively impact the client, may enable the CDMO to exceed expectations.

Experience and skills
Drug developers and sponsors should have access to the best talent. Experience and skills that the CDMO can offer. Great project managers will not only gain a complete understanding of the client's project, but they will also facilitate the assembly of a team optimally suited to the client's outcomes leveraging their knowledge of the CDMO internally. With more situational understanding than anyone else on the team, the project manager can facilitate collaboration across the CDMO's functional areas. For example, rather than pursuing a formulation recommended during concept development, a simpler formulation identified by the project manager could be less costly and developed faster.

Communication
To work efficiently on multiple projects simultaneously, CDMOs have unique, effective internal communications systems, but so do clients. Many times, these systems are not similar. Great CDMO project management operations modify communication and data sharing methods to meet the client's preferences.

Strategy
Project managers should have a focus on the overall objective— a long view of the project. The relationship between the project manager and the client should begin even before a contract or quality agreement is signed. Great project managers will ask questions that the client has not considered to avert problems and advance the work more quickly. The project manager facilitates onboarding, sets up the kick-off meeting, ensures key technical aspects of the project are clear, and communicates strategies within the scope of work.

Executive Involvement
Finally, great project managers have the visibility of senior decision-makers at the CDMO. They should meet internally with senior executives at the CDMO to review client projects — focusing on technology challenges, project milestones, and deliverables.

CDMOs should continuously improve their project management operations through the ongoing development of their project managers, both with formal education and training, and with company internal development programs.

Robotic Sterile Fill-Finish Machines

When producing a drug through the aseptic manufacturing process, the aseptic technique must meet cGMP standards. The pharmaceutical industry is evolving to reduce the risks of cross-contamination and consistently deliver sterility assurance. Automated, state-of-the-art, fill-finish suites reduce risks associated with operator engagement. Additionally, automated lines provide other benefits like:

- Efficiency
- Flexibility
- Precision
- Easier cGMP compliance

Specifically, when working with oxygen-sensitive products, the use of a robotic parenteral fill-finish machine can significantly improve and even eliminate oxygen exposure.

Examples of semi-automated to state-of-the-art, robotic, fully automated sterile filling machines.

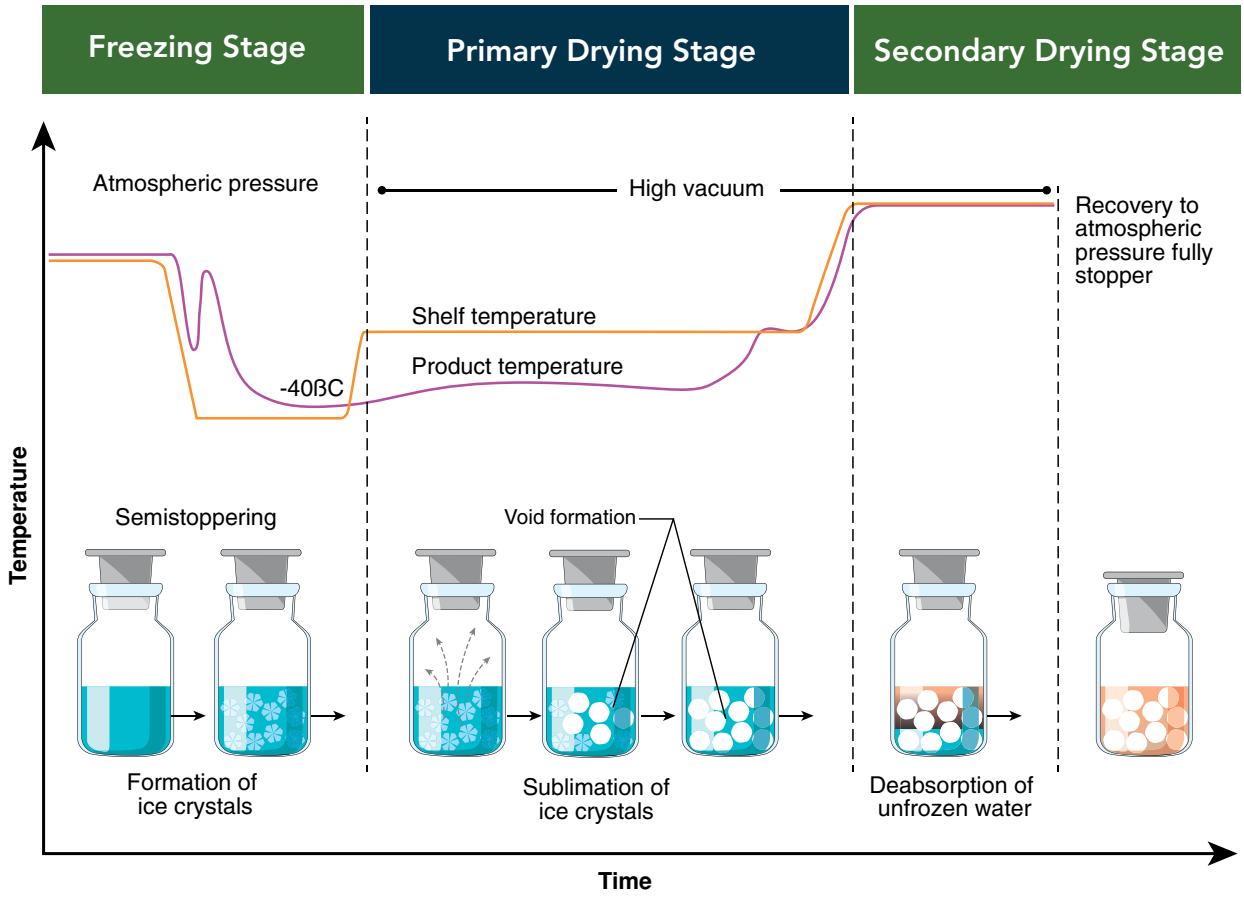
M&O Perry Vial Filling Machine:
This filling machine is equipped with a 2-head filler, peristaltic and rotary piston pump, and is capable of delivering inert gas. It can fill up to 40 vials per minute. It's also capable of filling 3mL-100mL vials and can handle up to 500-liter batch sizes.

Groninger Syringe Filling Machine:
This is equipped with a 2-head filler, rotary piston pump, and capable of delivering inert gas. The Groninger can fill 2400 syringes per hour.

Bosch FWR 4020:
This filling machine is equipped with an 8-head filler, rolling diaphragm pump, and capable of delivering inert gas. It can handle batch sizes up to 200,000 units with speeds up to 200 vials per minute. It is capable of filling 2mL-100mL vials and can handle up to 1000-liter batch sizes.

AST GENiSYS R:
This is the most versatile filling line for small batch production. This robotic, fully automated line minimizes human intervention between drug products and operators, greatly reducing the risk of contamination. It can fill vials, syringes, and cartridges up to 10K per day, 15-20 per minute. It can fill 2mL-30mL vials, 0.5mL-5mL syringes and 0.5mL-5mL cartridges.

Finally, these fill-finish machines should be situated in sterile rooms that allow for a seamless transition between the lyophilizer and the vial filling areas, and use a restricted-access barrier system (RABS).



Lyophilization Integration

Lyophilization, also known as cryodesiccation or freeze-drying, is a dehydration process used to stabilize formulations of sensitive or volatile parenteral drugs. Not all drugs require lyophilization. Maintaining aseptic conditions during lyophilization can pose a challenge. For this reason, lyophilization equipment need to be situated close enough to the filling equipment —minimizing the risk of contamination during transfer.

The most ideal way lyophilization is integrated into the sterile fill-finish process is by using

lyophilization equipment that is directly supported by the vial line of the sterile suite. In this, the vials are automatically filled and loaded into the lyophilizer.

"Experience tells us that for parenteral drugs, issues encountered are often associated with a lack of understanding of the functional relationships between formulation, processes, and the equipment. In lyophilization, these functional relationships must be well understood; otherwise the drug product quality attributes can be impacted," adds Bryan Braxton, Ph.D., Senior Director of Aseptic Research & Development at Pii.

The Millrock cGMP Lyophilizer is an example of a great lyophilizer that is directly supported by fill-finish machines such as the M&O Perry vial filling machine. It supports vial sizes between 3ml and 50ml and batch sizes up to 20,000 vials.

Scaling Sterile Fill-Finish Production

Agile organizations are more stable and reliable regardless of their size or how long they have been in business. The outcomes desired by pharmaceutical development require stability and reliability, as any disruption to the process is costly and can place the drug product and patients at risk. Add in the complexity and inherent risks associated with aseptic processes, and operational practices that deliver agility, stability, and reliability can be the difference between failure and success.

Scaling aseptic operations requires producing batches of drug products in ever-increasing sizes with quality. However, during preclinical and phase 1 development, the unknowns far outnumber the knowns. Will lyophilization be used to stabilize the drug product? What will the delivery mechanism be? Management capabilities with agility as a feature will keep the drug development process moving forward without disruption.

Critical capabilities and facilities needed for scaling aseptic production operations

• In-house lyophilizers and scientists skilled in developing lyophilization cycles, as aseptic formulations often require stabilization through freeze-drying.

• Fill-finish suites able to fill a variety of delivery devices: vials, pre-filled syringes, auto-injectors.

• Fill-finish suites that can produce varying batch sizes with adequate speed and under highly sterile conditions. Ideally, these suites are automated, limiting operator contact with the filling process.

Aseptic production and fill-finish operations are complex and unexpected challenges should be anticipated but not disrupt the outcome of delivering needed pharmaceutical products to patients. Agility is the key to rapidly and easily adapting to changes.

Regulatory cGMP

The Food and Drug Administration's (FDA) "Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice" is the most current cGMP guidance document for pharmaceutical manufacturers involved in aseptic processing.

It was created to help manufacturers meet the FDA cGMP requirements when manufacturing sterile drug and biological products using aseptic processing. It covers:

- Buildings and facilities
- Personnel training, qualification, and monitoring
- Components and containers/closures
- Endotoxin control
- Time limitations
- Validation of aseptic processing and sterilization
- Laboratory controls
- Sterility testing
- Batch record review: Process control documentation

Although the contents of the guidance document are non-binding legally, it is crucial to follow its recommendations, regardless of whether the drug or biologic is being produced in-house or in partnership with a cGMP certified CDMO. This will ensure that the drug product or biologic is safe for use in patients and contains the ingredients and potency it is intended to have.

Choosing the Right Partner for Your Sterile Fill-Finish Project

Aseptic manufacturing involves significant risks requiring proper mitigation to avoid patient safety consequences and regulatory issues. Accordingly, the choice of a CDMO partner for a sterile fill-finish project is a particularly important one.

Here are the approaches an ideal CDMO partner should take and the capabilities they should possess.

Approach

The CDMO partner should:

• Customize sterile fill-finish operations to suit the needs of the client.

• Create a scope for the sterile fill-finish project that is phase-appropriate and aligned with the client's resources and ultimately serves the patients. The CDMO should operate with empathy for the drug sponsor organization—recognizing how challenging it can be for executive leadership to achieve results cost-effectively.

• Rapidly gain an understanding of the client's needs and quickly define, at a high level, the scope, timeline, key milestones, and critical activities that will drive success.

• Work collaboratively with the client organization and with complete transparency.

• Assign a project manager for the lifecycle of the project to serve as an agent for the client.

Capabilities

The CDMO should:

• Have solid expertise and experience producing parenteral drugs using sterile fill-finish processes. More particularly, its professionals should have extensive experience working with complex, challenging sterile fill-finish projects that include highly viscous solutions and suspensions, highly sensitive formulations, and a variety of programs from small to large molecule.

• Possess facilities designed with vertically integrated capabilities that bring speed, agility, and quality to sterile fill-finish development and manufacturing.

• Have sterile fill-finish suites supported by a cGMP-scale lyophilizer and an analytical R&D lab, as well as a formulation and process development laboratory with lab-scale lyophilization services. This enables seamless scaling from development to manufacturing operations, delivering cost-effectiveness and saving time.

• Be able to easily and flexibly conduct sterile fill-finish operations for a wide range of containers, delivery systems, and batch sizes.

FAQs

What is aseptic drug manufacturing?
Aseptic Manufacturing and Sterile Fill-Finish is a process in which the drug product, container, and container closure are first sterilized separately and then brought together. The step of combining the product, container, and closure is done in a clean room and often uses special equipment that is self-contained in a sterile environment. The aseptic, sterile fill-finish process is challenging and complex.

What does aseptic mean?
Aseptic means that the product, delivery devices, and containers are free from contamination caused by harmful bacteria, viruses, or other microorganisms.

When is a sterile fill-finish pharmaceutical manufacturing process used?
A sterile manufacturing process is used for parenteral medicines because these products bypass the body's natural defenses against harmful bacteria and viruses. Drugs delivered by ophthalmic, inhaled, or otic routes also present an increased risk of infection or harm and are produced by sterile processes as well.

What is the difference between terminal sterilization and aseptic manufacturing?
Terminal sterilization is done after a drug has been manufactured and uses heat, radiation, and/or filtration. However, this is not always feasible and can have a detrimental effect on the product and its container. When terminal sterilization cannot be done, an aseptic manufacturing process is the preferred method. Aseptic manufacturing is a process in which the drug product, container, and container closure are first sterilized separately and then brought together. The step of combining the product, container, and closure is done in a clean room and often uses special equipment that is self-contained in a sterile environment.

Why is aseptic stability testing performed?
Stability testing provides evidence on how the quality of a drug substance or product varies over a given time and under the influence of environmental factors, including temperature, humidity, and light. All new drug products must undergo stability testing to meet the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1A(R2) requirements. The ICH Q1A (R2) document delineates the stability data package a new drug product needs to qualify it for a registration application.

Why is lyophilization used when producing parenteral drugs?
As complex drug products with stability issues become more common, and liquid dosage forms are not feasible, drug developers turn to sterile lyophilization. An effectively developed sterile lyophilization cycle can deliver stability for parenteral drugs over time and under a variety of environmental conditions during storage and transport.

What makes aseptic drug manufacturing so challenging?
Aseptic processing requires special equipment, highly trained, experienced people, and detailed planning and execution. The risks are significant for both the patient and production staff.
The process aims to eliminate contamination completely from the drug product, personnel, equipment, and facilities.

What regulatory guidance exists for sterile manufacturing?
In the U.S., the FDA's Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practices is the guidance available to help manufacturers meet the FDA's requirements. In Europe, EMA's "Guideline on the sterilization of the medicinal product, active substance, excipient, and primary container" is the guidance available for selecting appropriate sterilization methods for sterile products.

What are the cGMP requirements for pharmaceutical aseptic manufacturing?
The cGMP regulations for drugs contain the minimum requirements for the methods, facilities, and controls used to manufacture, process, and pack a drug product. The regulations make sure that a product is safe for use and that it has the ingredients and strength it claims to have.

Aseptic Fill-Finish Terminology

Vial -
A vial is a small glass or plastic vessel or bottle that stores medication as liquids, powders, or capsules. They can also be used as scientific sample vessels, for instance, in autosampler devices in analytical chromatography.

Syringe -
A device used to inject drugs into the body or withdraw fluids from it. It is typically made up of a hollow tube fitted with a pump system with a piston for drawing in and ejecting fluid. A needle is attached to the end of a syringe to penetrate the body's tissues.

Cartridge -
This is a primary packaging container that is typically used with injector pens or other self injecting systems. Like syringes, cartridges can come prefilled.

Vaccine -
A vaccine is a biological preparation that provides active-acquired immunity to a particular infectious disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins.

Sterile -
Sterile compounded medications are intended to be used as injections, infusions, or applications to the eye. Non-sterile medications include the production of solutions, suspensions, ointments, creams, powders, suppositories, capsules, and tablets.

Injectable -
This refers to any drug or biologic that can be introduced into the bloodstream using a needle and a syringe.

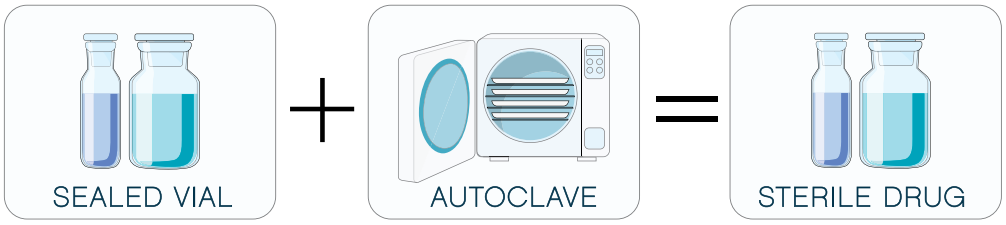
Parenteral -
This is a method of administering drugs that involves non-oral means. Most parenteral drugs are injected into the body intramuscularly, subcutaneously or intravenously.

Biologics -
Biologics can be composed of living entities such as cells and tissues or sugars, proteins, nucleic acids, or a combination of these substances. Biologics are isolated from a variety of natural sources - human, animal, or microorganism - and may be produced by biotechnology methods and other cutting-edge technologies. Biologics include vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.

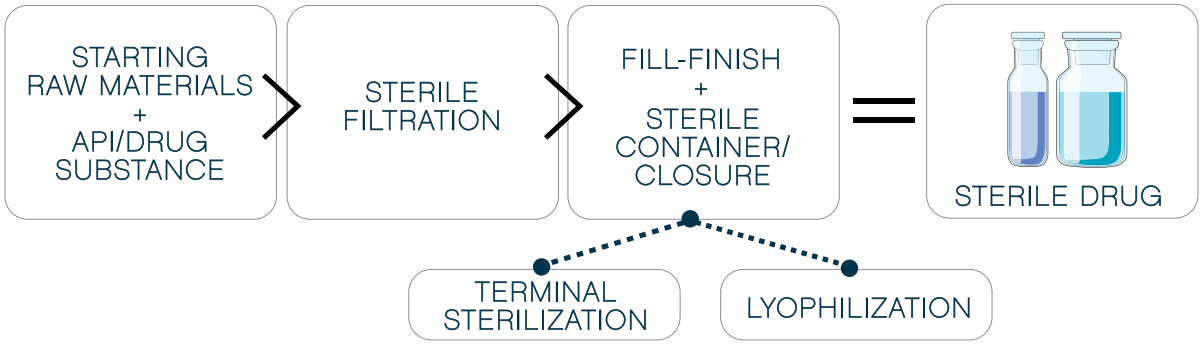
Cleanroom -
A room designed and maintained to prevent particles and microbes from contaminating drug products.

CDMO -
A contract development and manufacturing organization (CDMO) is a company that offers drug development and manufacturing services to pharmaceutical companies desirous of outsourcing these processes.

TERMINAL STERILIZATION PROCESS



ASEPTIC PROCESSING



Terminal Sterilization

Terminal sterilization is the process of sterilizing a drug product after the formulation and filling process in the final primary container. The terminal sterilization process should be validated as it is an important process as it ensures the product remains sterile. A sterile product contains no living organisms. The two most common methods used to manufacture sterile products are terminal sterilization and aseptic processing.

Terminal sterilization can be done in different ways, and the selection of an appropriate one depends on the properties of the drug substance. Some terminal sterilization methods include moist heat/steam sterilization, irradiation, and hydrogen peroxide vapor sterilization. Moist heat sterilization is the method most commonly used, and it involves placing the filled, tightly sealed containers into an autoclave. Exposure time, temperature, moisture, air removal, and drying are critical factors in this terminal sterilization process.

Terminal sterilization is the preferred sterilization method for parenteral drug manufacturing. When terminal sterilization is not an option, aseptic processing is used.

Pii

Pharmaceutics International, Inc

Challenges Frame Opportunities

Pharmaceutics International, Inc. (Pii) is a science-driven contract development and manufacturing organization (CDMO) with a single campus in Hunt Valley, MD, USA, offering unparalleled scientific insight and depth of product knowledge while supplying high-quality dosage forms that enhance the lives of patients worldwide.

Founded in 1994, Pii has grown from 12 employees to over 280 scientists and support staff and over 360,000 square feet of space in the U.S. Pii's cGMP facilities are state-of-the-art and contain over 70 manufacturing rooms as well as containment suites for handling high potency compounds and hormones, dedicated manufacturing suites for oral products (e.g., soft gels) and injectables (e.g., vials and syringes), a formulation development center and state-of-the-art analytical laboratories.

Flexibility
We understand that designing an efficient drug delivery system cannot be successful with a "one-size-fits-all" approach. It is critical to tailor the development process to the characteristics of the drug or biologic and the development goals of the client.

Innovation
Pii strives to be a reliable and flexible partner by responding and adapting to the individual needs of each client. From project kick-off through close-out, our focus is to exceed your expectations by providing a high level of customer service.

Quality
At Pii, we are never satisfied with where we are today; instead, we are focused on meeting tomorrow's regulatory expectations. We continuously invest in understanding regulatory requirements, adopting best practices and maintaining credibility with regulatory authorities.

Science
People are the foundation of the service we provide. Pii's team is comprised of seasoned industry leaders and highly educated experienced scientists who have "walked in your shoes." They bring their deep scientific know-how and diverse backgrounds to every project and work with you to produce practical and creative solutions.

Kurt Nielsen, Ph.D., *President and CEO*
Kurt Nielsen joined Pii in 2019 as President and CEO. Dr. Nielsen is a seasoned pharmaceutical executive with over 20 years of diverse experience, most recently as the President of Lupin Somerset, responsible for all its generic and branded products. Prior to Lupin, he held the post of Vice President, U.S. Development, Portfolio and Launch Management at Sandoz Inc., where he was accountable for the U.S. development of generic, OTC and specialty brand products. Dr. Nielsen has also held positions at Catalent, where he was Senior Vice President of R&D and Chief Technology Officer, and URL Pharma where he was the Executive Vice President, Pharmaceuticals.

John Guthrie, *Chief Financial Officer*
John Guthrie is Chief Financial Officer at Pii. Prior to Pii, John was Managing Director and Chief Operating Officer of Motir DuSable Power Investments, a renewable energy company focused on Sub-Saharan Africa. In earlier years he served in CFO roles in the technology, printing and plastics industries and began his career at Deloitte.

Monique Mendoza, *Head of Quality*
Monique Mendoza is the Head of Quality at Pii and has over 20 years of experience in the pharmaceutica/biotechnology industry. She is responsible for the entire quality unit at Pii. Her responsibilities include Quality Assurance & Control, Batch Disposition, Investigations, Change Controls, Product Complaints, Supplier Qualification, Raw Material Release, Audits, Document Control. Monique earned her B.S. from the University of the Pacific.

Kevin Kelly, *Head of Sales*
As the Head of Sales, Kevin Kelly works closely with the scientists and leaders of Pii to drive successful projects. With his industry knowledge, Kevin is able to specialize in challenging projects and manufacturing processes. His specialties include formulation development, CTM manufacture, analytical method development and validation, and process development. Kevin graduated from Drexel University with a Bachelor of Science in Business Administration and Marketing.

Shawn Watson, *Head of Research and Development*
Shawn Watson is responsible for all product development, including sterile, non-sterile, oral, and topical dosage forms, as well as analytical methods development. He has additional responsibilities for the Quality Control and Microbiology Laboratories. Shawn has over twenty years of leadership experience in the pharmaceutical industry in specialty, generic, and contract development and manufacturing organizations (CDMOs).

Roberto Almodóvar Febles, *Head of Aseptic Operations*
Roberto Almodóvar Febles brings more than 15 years of progressive experience in manufacturing management, organizational development, process improvement/development technical support, and quality assurance experience to his role as Head of Aseptic Operations at Pii. Prior to joining Pii, he supported programs at many world-class pharmaceutical companies, including Baxter Healthcare, Amgen, iPR Pharmaceuticals (the CMO for AstraZeneca), and Mylan. Mr. Febles has experience in Lean Six Sigma, Tech Transfer, Gap Analysis and Risk Assessment, Project Management, and Warning Letter Remediation, as well as extensive knowledge of regulatory stanards.

Devan Patel, *Senior Director, Project Management*
Devan Patel leads key development and commercial programs for Pii for both the orals and injectables. Devan plays a vital role for the Operations team, managing key initiatives for the Parenteral/Sterile business unit, managing scheduling and planning of Aseptic Operations. His works with cross-functional teams across Pii's business units to anticipate problems before they occur. Devan earned his Bachelors in Cell Biology and Molecular Genetics from the University of Maryland and a M.B.A. from Johns Hopkins University.

PJ Kim, *Head of Commercial and Corporate Development*
PJ Kim is the Head of Commercial and Corporate Development, with 17 years of experience in the pharmaceutical industry. PJ has worked in the pharmaceutical industry as an Account Manager, Regulatory and Quality Manager, and Overseeing IND Studies. PJ earned his bachelors in Biology from Case Western Reserve University, and Masters in Business from Baldwin Wallace University.

Sheryl Basile, *Vice President of Human Resources*
Sheryl Basile has over 20 years of human resources experience including Halo Pharma where she led the HR function and most recently as Director of HR for Lupin Pharmaceuticals's Somerset site. Sheryl brings broad human resource experience with a business focus and partnership skills, including Talent Management, Coaching, Employee Relations, Immigration, Performance Management, and Compensation Analysis.

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