

Good Working Practice – Manufacturing

1. Inspecting for Manufacturing and Packaging Defects-Aseptic

Sterile Drug Products and Sterile Medical Devices shall undergo inspection for manufacturing and packaging defects, after the drug product or medical device Containers are sealed. Qualified personnel authorized by the Site Quality Team shall perform the inspections as follows:

For Human Injectable or Implantable Products:

- A 100 percent inspection, on-line or off-line, of each sterile unit; and
- A second inspection, based on an Approved statistical sampling plan. For Human Ophthalmic Products, Topical Ointments, and Animal Health Products:
- An on-line or off-line inspection based on an approved statistical sampling plan.

This practice applies to GMP Production Sites performing aseptic manufacturing and packaging of sterile drug products, biologics, and sterile medical devices for Pharmaceutical, Animal Health.

Manufacturing and Packaging Defect Categories shall be established and include:

- Critical Defects,
- Major Defects, and
- Minor Defects.

Drug Products and Medical Devices shall be inspected for manufacturing and packaging defects using one or both of the following methods:

- Visual inspection, and/or
- Automated electronic system inspection. An Acceptable Quality Level (AQL) shall be established based on historical performance for each drug product and medical device at each plant Site for the following:
- Each defect category (i.e., critical, major, and minor); and
- Total number of defects found in the Batch/Lot.

Manufacturing and Packaging Defects shall be documented and Trended for each drug product, medical device, and container/Closure configuration. Automated Electronic Inspection Systems shall be Commissioned and/or Qualified.

Inspection Procedures must be written and approved and must include, at least, the following information:

- Inspection techniques for each type of drug product, medical device, and container/closure configuration;
- Unique characteristics of the drug product or medical device; and
- Physical attributes that are considered defects.

Product Units shall be inspected for defects including, and not limited to, the following:

Drug Product in Glass or Plastic Containers

- Cracked or chipped containers;

Good Working Practice – Manufacturing

- Establishment of critical process parameter Operating Ranges; and
- Verification of proper machine operation and that specific defects (e.g., fill volume, particulates) are identified and rejected based on the sensitivity setting.

Performance Qualification (PQ) for Automated Electronic Inspection Systems shall include, and is not limited to, the following test:

1. Set the equipment to operate within the established critical process parameter ranges for the product and container/closure configuration to be inspected;
2. Place a known quantity of defects that represent the typical reject types in a defined number of product units;
3. Verify that the pre-defined number or percentage of defects was identified at the completion of the inspection;
4. Inspect the same product units using visual inspection procedures;
5. Verify that the automated inspection results are at least as accurate as the visual inspection results;
6. Verify that the number or percentage of acceptable product units that are rejected by the automated electronic inspection system does not exceed a pre-determined acceptance limit (e.g., < 1.5%); and
7. Repeat the qualification a minimum of three times.

Set-Up Procedures for Automated Electronic System Inspection Equipment shall include the inspection of a medical device or drug product test set, having a known quantity of defects, prior to inspecting every batch/lot of medical device or drug product. Inspection of the test set shall result in the rejection of the known defective units.

Visual Inspection Station Design shall include, and not be limited to, the following:

- Light source (e.g., fluorescent, tindell beam, polarized) with an intensity of 100 to 350 foot-candles;
- Light positioned above, below, or behind the units to be inspected; • Glare minimized;
- Matte black and matte white inspection backgrounds;
- Comfortable environment;
- Easy access to product units; and
- Designated areas for rejected and acceptable units.

Visual Inspection Station Maintenance shall include, and not be limited to, the following:

- Inspection background cleaned according to an approved schedule;
- Light source intensity periodically monitored and the light source replaced as needed;
- Inspection area clearly identified during inspections with product identification and Batch or Lot Number; and
- Inspection area cleared of all unrelated product units, using line clearance procedures, after the completion of the inspection.

Good Working Practice – Manufacturing

- Processing instructions, including sequences to be followed, Critical Process Parameter Ranges, sampling instructions, In-Process Controls (IPC) and acceptance criteria, and time limits for completion of critical processing steps and/or the total process;
- Instruction or reference to instructions for the storage of product including the container, Labeling, and any special storage conditions; and
- Any special precautions (e.g., protective equipment, gowning requirements).

Master Manufacturing Instructions for Drug Products shall include, and are not limited to, the following information:

- Product name, strength, and identification code;
- Batch or lot size;
- Description of dosage form;
- Name and weight or volume of each API per dosage unit or per unit weight or volume of product;
- Total weight or volume of dosage unit;
- A complete list of components, designated by names, and/or codes sufficiently specific to indicate any special quality characteristics (e.g., grade);
- Accurate statement of the weight or volume of each component;
- A statement concerning any calculated excess of a component;
- Statement of theoretical weight or measure and Accountability for components and product at critical phases of processing;
- Statement of expected yield including the maximum and minimum percentages of theoretical yield beyond which an investigation must be conducted;
- Instructions or reference to instructions to be used for preparing the critical equipment (e.g., cleaning, assembling, sterilizing);
- Processing instructions, including detailed stepwise instructions, critical process parameter ranges, sampling instructions, in-process controls and acceptance criteria, and time limits for completion of critical processing steps and/or the total process;
- Description of storage requirements for product including the container, labeling, and any special storage conditions; and
- Any special precautions (e.g., protective equipment, gowning requirements).

Manufacturing Batch Records shall be created from the Master Manufacturing Instructions and shall be used to record activities associated with manufacturing the batch.

Manufacturing Batch Records for APIs shall be used to document the completion of each significant step during the manufacturing of the batch or lot, and shall include and are not limited to:

- Unique batch identification;
- Dates and times (if required) for each significant step
- Identity of Major Equipment (e.g., reactors, driers, mills) used;
- Weights, measures, and Batch Number or Lot Numbers of raw materials, intermediates, or any Reprocessed materials used during manufacturing;
- Actual results recorded for Critical Process Parameters;
- Any sampling performed;

Good Working Practice – Manufacturing

- Practice of aseptic technique and applicable aseptic interventions (e.g., not blocking airflow, use of forceps, carrying materials in APA, aseptic set-up and connections, and proper movement and behaviour); and
- Demonstration of airlock practices.

Skills Based Training in Gowning for APA Personnel or APA Support Personnel shall include, but is not limited to:

- Demonstration by trainee of proper gowning techniques; and
- Pass environmental monitoring of gloves and gown

Criteria for Initial Qualification of APA Personnel and APA Support Personnel shall include:

- Knowledge based training;
- Successful demonstration of gowning technique in accordance with Standard Operating Procedures (SOP);
- Three (3) consecutive, acceptable gown and glove testing results conducted after gowning ; and
- Skills based training on applicable job skills including demonstration of competence; and
- Participation in a successful aseptic processing simulation including performance of predefined job skills.

Criteria for Annual Re-Qualification of APA Personnel and APA Support Personnel shall include:

- Knowledge based training (i.e., review of material focusing on areas of concern or interest for area/department, information to build on existing knowledge level of personnel);
- Successful demonstration of gowning technique in accordance with SOPs;
- Acceptable gown and glove testing results;
- Skills based training on applicable job skills including demonstration of competence, if identified in Risk Assessment; and
- Participation in a successful aseptic processing simulation including performance of predefined job skills.

Re-Qualification Training shall be given to APA Personnel and APA Support Personnel when an employee has not worked in the APA for a defined time period as determined by a documented Site risk-based analysis. Such re-qualification shall include:

- Review of knowledge based training;
- Successful demonstration of gowning technique in accordance with SOPs;
- Acceptable gown and glove testing results;
- Skills based training on applicable job skills including demonstration of competence; and
- Participation in a successful aseptic processing simulation including performance of predefined job skills.

Visiting Personnel shall complete the following prior to being escorted in the APA:

- Training in applicable Site SOPs including gowning practices; and
- Successfully pass one gown and glove monitoring.

Good Working Practice – Manufacturing

- Locations likely to be difficult to clean and sanitize;
- Historical data;
- Qualification data;
- Production activities;
- Line configuration; and
- Personnel, product, and/or material traffic patterns.

The Environmental Monitoring Program shall include documentation of sampling locations including:

- Area diagrams with sampling locations;
- Type and frequency of sampling at each sampling location, including provisions for sample rotation;
- Microbiological monitoring of all sites in Grade A through Grade D areas during in operation conditions. This includes set-up in Grade A areas; and
- Provisions for sampling additional locations at the discretion of the sampler, including documentation of sampling location and reason for selecting the site.

Microbiological Environmental Sampling Results shall be reviewed by the Site Quality Team within one business day of data being recorded.

Microbiological Environmental Sampling and Personnel Monitoring shall be performed by qualified personnel authorized by the Site Quality Team. The practice of unobserved self-sampling is not allowed.

Total Airborne Particulate Monitoring shall be performed by qualified personnel authorized by the Site Quality Team. The Site Production Team and the Site Quality Team shall review the data.

Microbiological Environmental Monitoring, Personnel Monitoring, Temperature, Humidity, and Pressure Differential Data shall be tabulated and trended using tools such as spreadsheets, graphs, or charts, to show cumulative data and highlight all alert and action levels.

Microbiological Environmental Monitoring Trends shall be analyzed by the Site Quality Team for:

- Increases and decreases in Microbial Populations over time;
- Changes in the types of microorganisms identified;
- Need for increased or decreased monitoring;
- Establishment of alert and action levels (expected absence of microbial growth for Grade A areas);
- Need to change alert and action levels [alert and action levels shall only be lowered (i.e., tightened) based on historical data]; and
- Need to recertify or retrain individuals in personnel gowning practices.

Microorganisms isolated from the environment shall be characterized as follows:

- Bacteria and yeast microorganisms shall be characterized to species level when isolated from Grade A or B (Grade A background) and from personnel glove and gown samples, and when action levels are exceeded in any areas. An identification scheme shall be designed to identify microorganisms to the

Good Working Practice – Manufacturing

In-House Prepared Microbiological Culture Media shall be:

- Suitable for the detection of microorganisms (e.g., SDA or TSA) and when necessary (i.e., if used in areas where product might inhibit growth) contain neutralizers to inactivate sanitizers and/or antimicrobial drug products;
- Used only after it has been approved for use upon successful growth promotion testing;
- Stored under validated conditions;
- Inspected for visible microbial contamination prior to use;
- Incubated as quickly as possible with the time between exposure and incubation not to exceed twelve (12) hours unless supported by data; and
- Used within its laboratory qualified expiration date.

Separate Microbiological Growth Media shall be used for the detection of bacteria and a differential medium for the detection of fungi (e.g., SDA). Exposed media shall be incubated and monitored as follows:

- Bacteria specific media at 30 -35°C for a minimum of five (5) calendar days;
- Fungi specific media at 20 -25°C for a minimum of five (5) calendar days; and
- Check for growth, at least, at the end of the incubation period.

Growth Promotion Testing shall be performed successfully on all lots of prepared media prior to being approved for use. Testing must demonstrate that the media can support the growth of a selected panel of microorganisms that includes, at least, one microorganism found in the environment.

An Environmental Monitoring Report, which might prompt an investigation and corrective actions, shall be completed when environmental conditions exceed specified alert or action level ranges. Such reports shall be included in all batch/lot records or DHRs potentially affected. The report shall include a complete sample description (e.g., location, type of sample, test results, affected lot/batch).

An Investigation shall be conducted whenever an action level is exceeded. The investigation shall include, and not be limited to:

- Identification, if possible, to the species level of microorganism(s) associated with an action level;
- Establish, if possible, a cause and effect relationship between the observed growth and possible source(s) of contamination;
- Corrective action measures;
- Identification of any additional lots or batches which may be impacted; and
- A completed investigation approved by the Site Quality Team and Site Production Team within thirty (30) calendar days and prior to lot/batch release.

If the investigation will go beyond thirty (30) calendar days, an interim status report must be issued by the Lab Supervisor to the Site Quality Team.

Each Environmental Sample shall be labeled with a unique identification code that is traceable to the environmental sampling record.

Good Working Practice – Manufacturing

When Establishing Impurity Limits for Recovered Solvents Intended for General Site-Wide Use, the following must be considered:

- Capability of the solvent recovery equipment and process;
- The volatility of potential contaminants (e.g., other solvent impurities, reactants, intermediates, and side products); and
- The potential for contaminants to be carried over in the recovered solvent.

For External Contract Vendors of Recovered Solvents to a Site, the responsible Site Quality Team shall assure that the methods, facilities, and controls (e.g., measures for storage, loading, shipping, and unloading of the recovered solvent) used by the contract vendor meet the requirements in this document including, and not limited to, the following:

- Site Audit Report available indicating acceptability;
- Contract approved by both parties;
- Quality Agreement;
- History of use, if the equipment is used to recover solvents from non-Site firms;
- Acceptable cleaning of equipment; and
- Solvents must meet Site specifications.

Virgin and Recovered Solvents can be combined if testing has shown that each is suitable for all manufacturing processes in which they are intended to be used. If approved recovered solvent is mixed with virgin solvent, the mixture shall be restricted to the approved uses of the recovered solvent.

Solvent Recovery and Recycle Processes must be described and documented in approved Instruction-Records, which include, and are not limited to:

- A description of the processing steps, including the order in which they are conducted;
- Solvent characteristics;
- Any testing (in-process and/or release) performed, including specifications;
- Process Parameters;
- Process parameter ranges;
- Description of materials, including quality and quantity, used in the processing of the solvent (e.g., pretreatment materials, entrainers);
- Equipment used for the recovery; and
- Any recovery or recycle equipment preparations.

In-Process Controls (IPC), if performed, shall meet acceptance criteria that are designed to ensure the recovered solvents are suitable for their intended use.

Routine Analytical Tests must be used to demonstrate that each recovered solvent Lot meets its established release specifications. Such analytical tests must be Validated.

Direct Impact Solvent Distribution and Storage Systems shall meet Qualification requirements. Design of such systems shall include consideration of, and is not limited to, the following:

- Material(s) of construction; and

Good Working Practice – Manufacturing

All Product Contact Parts of metal detectors shall be cleaned after use, following a Validated cleaning process. Equipment shall be removed from the manufacturing or packaging line, when possible, for cleaning.

8. Weighing and Measuring Practices in Manufacturing Operations

This practice document applies to weighing and measuring of materials used in the manufacture of Drug Products, Active Pharmaceutical Ingredients (API), Medical Devices, and Intermediates.

This document applies to all GMP sites where intermediates, APIs, drug products, and medical devices are produced for Pharmaceutical or Animal Health.

System shall be established and maintained at the site to assure that materials (e.g., Starting Materials, Raw Materials (RM), and APIs) used in the manufacturing process are weighed or measured under conditions that will not affect the fitness-for-use of the material in the manufacturing process.

For materials which do not require Subdividing, and are purchased from Approved Suppliers with weighing practices that have been audited and found acceptable to Site, the weight indicated on the Container label by the Supplier may be accepted in lieu of reweighing and transferring the materials to another container.

Methods for Weighing and Measuring Materials shall be established and maintained according to Standard Operating Procedures (SOP) and shall be Approved by the Site Quality Team and Production Team.

Methods for Weighing and Measuring shall be accurate and repeatable over the range of weights or measures for which the methods are used.

Weighing and Measuring Operations shall be performed by Qualified personnel.

Containers of Weighed or Measured Materials Being Dispensed for Manufacturing Use shall be labeled to clearly identify the contents and any special handling requirements.

The Identities and Actual Quantities of Materials being prepared for manufacturing use, unless determined by a Validated automated system, must be Verified by a second person (commonly known as a Dual Witness).

Actual Quantities of Materials Used in the Course of Processing shall be documented in the Manufacturing Batch Records for the API or drug product, or in the Device History Record (DHR) for the medical device.

Routine Calibration, Periodic Operational Checks, and Maintenance of scales and balances and cleaning of dispensing modules or areas shall be conducted and documented according to approved schedules and procedures.

Good Working Practice – Manufacturing

- Method VD_{MAX}-substantiating use of selected radiation doses of either 15kGy or 25kGy.

Pre-Sterilization Bioburden of APIs, Drug Products, Medical Devices, and Non-Product Items shall be minimized and controlled. The bioburden shall be determined as defined by the radiation dose setting method that is used, and monitored at an established frequency, not to exceed 12 months, defined in a written Site Standard Operating Procedure (SOP).

Dosimeters shall be used during validation studies and routinely to monitor absorbed radiation dose.

Each Batch/Lot of Dosimeters shall be supplied with a Certificate of Analysis (COA) and prior to use shall be:

- Calibrated; and
- Approved for use by the contract facility Quality Team.

An Audit of the Dosimeter Manufacturer(s) shall be conducted by the contract facility Quality Team and shall establish the acceptability of the manufacturer's validation studies, operations, and facilities.

The Irradiation Source shall be monitored for source decay and the performance documented (e.g., process control chart), at least weekly, to ensure that the required dose range is delivered during gamma radiation sterilization.

Instruments and Elements (I/E), including dosimeters, used to monitor or control gamma radiation sterilization processes shall be calibrated according to an approved schedule.

Gamma Radiation Facilities shall have material handling procedures in place that are designed to preclude the mix-up of irradiated and non-irradiated items.

Mixed loads containing more than one batch or lot of material within one irradiation carrier or container are prohibited.

Additional Exposure to Sterilization Conditions or Reprocessing (e.g., as a result of an aborted cycle or mechanical failure) must be approved by the Site Quality Team and supported by validation studies that provide documented evidence that the long-term product stability is unaffected by additional processing. Total exposure shall not exceed the maximum validated limit of the radiation dose.

Irradiator Dose Mapping Studies shall be conducted to characterize the irradiator with respect to the magnitude, distribution, and reproducibility of dose delivery. Irradiator dose mapping shall be performed:

- On each conveyor path or batch chamber;
- Using irradiation carriers filled to their design limits with material of a homogenous density (e.g., simulated product or a representative product of uniform density) within the limits of the bulk density range for which the irradiator is to be used;

Good Working Practice – Manufacturing

- HVAC systems;
- Water systems; and
- Drainage systems.

Materials and Products shall be handled in a manner designed to prevent uncontrolled release of dust, gases, vapours, sprays, or microorganisms into the production environment.

Standard Operating Procedures (SOP) shall be established at each Site to minimize cross contamination and shall address, and not be limited to, the following items:

- Material storage and flow;
- Sampling;
- Personnel gowning, practices, and flow;
- Cleaning and line clearance;
- Handling of spills;
- Equipment usage, storage, and flow; and
- Environmental requirements (e.g., dust, microorganisms, Pressure Differentials, airflow).

Special Containment Measures, such as Special Precautions, Dedicated Manufacturing Suites, or Dedicated Manufacturing Facilities shall be taken to prevent cross contamination where trace presence of one product [e.g., Occupational Exposure Band (OEB) classification 4 or classification 5 products, beta-lactams, and Cytotoxics] could have serious consequences on patients taking another product. This policy does not apply to facilities that are dedicated to animal health products.

Live Microorganisms and Biological Preparations shall be manufactured, transferred, sampled, and packaged in closed or contained systems in separate or defined areas to prevent cross contamination.

Personnel shall not pass through areas, where exposure to live organisms or animals is possible, to access Production Areas where other exposed products or different organisms are handled. If such passage is unavoidable, clearly defined decontamination measures shall be followed, including changes of clothing and shoes and, where necessary, showering.

Centrifugation and Blending of Products Containing Live Microorganisms, which can lead to aerosol formation, shall be contained to prevent release of live microorganisms.

Delivery, Receipt, Sampling and Testing of Bulk Materials (e.g., Tankers Delivery) shall be performed according to SOPs designed to minimize cross contamination.

Product Changeover Cleaning Procedures must be Validated Pesticides and Herbicides shall not be produced or stored in the same facilities as those used for the manufacture and storage of APIs, intermediates, in-process materials, drug products, or medical devices.

Good Working Practice – Manufacturing

Operational Qualification (OQ)/PQ runs.

Each Lot of Commercially Prepared BIs shall have a Certificate of Analysis (COA) from the manufacturer.

Custom Prepared BIs for Moist Heat Sterilization or dry heat sterilization shall be tested prior to use for:

- Spore population; and
- *D*-value.

When BI Spore Suspensions are Directly Inoculated onto Components (e.g., Closures) or Equipment for moist or dry heat sterilization, the *D*-value must be tested after inoculation of the spore suspensions onto the substrate.

Steam Sterilization Critical Process Parameters shall include temperature, pressure, and exposure time.

Clean Steam shall be used in steam sterilization processes, shall be routinely tested, and shall meet specifications for chemical and biological attributes.

Steam Sterilization Cycle Development shall include the following:

- Verification of steam saturation using a temperature/pressure correlation table;
- Calculation of F_0 in the coolest location in the load (from temperature mapping studies) to determine the degree of lethality as a function of Process Parameters;

For Steam Sterilization Processes, if load probes are present in the sterilizer, the placement of the probes shall be established during validation studies and the data generated during a run shall be reviewed against specifications.

Vacuum Leak Tests shall be conducted during qualification studies on steam sterilizers and included in the PM program.

The Bowie Dick Test (e.g., see ANSI/AAMI/ISO 11134: 1993 – Ref 10) or equivalent shall be performed on steam sterilizers that use vacuum cycles, at least quarterly, to ensure that the specified vacuum is achieved in the steam sterilization unit.

DH Sterilization and Depyrogenation Critical Process Parameters shall include temperature and exposure time.

DH Sterilization and Depyrogenation Equipment shall be designed and equipped with HEPA filtered air and designed to operate at an overpressure to the surrounding environment for the following types of units:

- Forced air convection ovens, and
- Continuous belt dry heat tunnels.

DH Depyrogenation Cycle Development shall include the following:

- Runs conducted using EIs;
- Diagram of the placement of EIs; and
- A three (3) log reduction in Bacterial Endotoxin as demonstrated by Bacterial Endotoxin Testing (BET).

Good Working Practice – Manufacturing

In the Event of a Facility Evacuation (e.g., fire drill), APA Personnel, APA Support Personnel, PAA Personnel and PAA Support Personnel shall, upon returning to the building after evacuation, re-gown prior to reentering the APA or PAA following the gowning procedures defined in this practice. When area-dedicated shoes are worn outside of the building, shoe covers shall be worn over area-dedicated shoes until the area-dedicated shoes can be Disinfected or replaced with another pair of area-dedicated shoes.

APA Personnel, APA Support Personnel, PAA Personnel, or PAA Support Personnel with an apparent illness or open lesion shall contact the responsible APA or PAA

Supervisor for reassignment outside of the APA or PAA. Illnesses (as determined by medical examination or supervisory observation) that shall preclude entering the APA or PAA include, and are not limited to, the following:

- Upper respiratory infections;
- Gastrointestinal infections;
- Influenza; and
- Skin conditions (e.g., severe sunburn, psoriasis, open sores).

Visiting personnel with an apparent illness or open lesion shall not enter the PAA or APA.

Personnel Working or Visiting Personnel in the APA or PAA shall:

- Practice good hygiene, as outlined during training;
- Not wear jewelry, except for a smooth wedding band;
- Not wear makeup;
- Not wear false eyelashes;
- Minimize facial hair;
- Cover hair completely with hair covers (including facial hair);
- Keep nails short, not wear nail polish, and not wear artificial nails; and
- Wear goggles in APA, or eye protection (e.g., safety glasses with side shields) in PAA.

APA Gowns shall be made of non-linting and non-static producing material. Sterilized gowning articles shall be packaged in non-shedding, non-cellulose packages.

PAA Secondary Garments shall be made of non-linting and non-static producing materials with elasticized wrists such as a clean lint-free lab coat or disposable garment (e.g., Tyvek). -Studies shall be conducted to demonstrate the number of times reusable gowns can be cleaned and sterilized, if applicable, before being discarded. A system for tracking the number of gown cleanings and sterilizations shall be implemented.

Gowning and Degowning for the PAA shall be performed in a gowning/degowning room adjacent to the PAA. Fresh, protective clothing shall be stored neatly in bins and/or on racks. The PAA gowning/degowning room shall be equipped with a bench and hand-washing facilities or a dispenser containing sanitizer. Gowning for the PAA shall be performed as follows:

Good Working Practice – Manufacturing

containers. The maximum allowable time that containers and closures are held at sterilization or depyrogenation conditions shall be established and validated.

The Maximum Allowable Number of Times that Rubber Stoppers can be sterilized shall be validated to include effects on:

- The physical and chemical properties of the elastomer; and
- The Container Closure System integrity and product stability.

Containers, Closures, Cleaning Agents, and Silicone Fluid shall be received in the same manner as Raw Materials. Inspection and/or testing and release requirements for these materials shall be defined by Specifications.

Materials Such as Silicone Fluid and Cleaning Agents used in connection with containers and closures prior to sterilization shall be controlled to minimize microbial, particulate, and endotoxin contamination.

The Pre-Sterilization Bioburden of Containers and Closures shall be controlled to a consistently low level when non-thermal processes are used for sterilization (e.g., radiation, ethylene oxide).

Manufacturers and Suppliers responsible for washing and/or sterilizing containers and closures shall be approved following the supplier approval process.

The Maximum Time Interval Allowed Between Washing and Sterilization of containers and closures and the maximum time interval allowed between sterilization and use of the containers and closures shall be validated.

The Flow of Sterile Containers and Closures into the Aseptic Processing Area (APA) shall be unidirectional. Sterile containers and closures shall be delivered to the APA in a manner designed to prevent contamination, such as through double-sided Batch sterilizers, continuous sterilization/depyrogenation tunnels, or Airlocks.

Measures to Differentiate sterile containers and closures from non-sterile containers and closures shall be defined; examples of these measures include:

- Supplier identification of sterile items,
- Sterilization indicators,
- Facility design, and
- Procedures for handling containers and closures before and after sterilization.

Cleaned Containers and Closures shall be protected from contamination prior to sterilization.

Sterilized Packaged Containers and Closures shall be visually inspected for damage to the package prior to storage or use.

Personnel Washing and Sterilizing Containers and Closures shall be Qualified and follow the gowning practices for Preparation for Aseptic Areas (PAA) personnel.

Good Working Practice – Manufacturing

Membrane Filters with a porosity no greater than a nominal 0.22 micron shall be used as sterilizing filters. In cases where microorganisms are not retained by 0.22 micron filters, 0.1 micron filters shall be used (e.g., Mycoplasma sp.).

Pre-filtration Bioburden of Sterile APIs, Sterile Medical Devices, and Sterile Drug Products shall be determined using a Validated Test Method (TM), monitored, minimized, and controlled.

Steam Sterilization Cycles for Filters, *in situ*, shall be validated using thermocouples and Biological Indicators (BI) located on the upstream and downstream sides of the filter. Steam sterilization cycles for filters sterilized in autoclaves shall be conducted.

Asbestos Containing Filters must never be used.

Sterile Filtration of APIs, drug products, medical devices, compressed gases, and solvents through the Final Filter shall be driven by positive pressure. Vacuum driven filtration shall not be used for sterilization except for use of vent filters.

The Maximum Use Interval for a Sterilizing Filter, in terms of days in use, sterilization cycles, or the number of Batches/Lots processed, must be validated if the filter is to be used in manufacture of sterile APIs, drug products, medical devices, or in sterilizing water or other solvents. When the validated limit is reached, the filter must be replaced.

Sterilizing Grade Filters shall be Integrity Tested and the integrity test (e.g., Bubble Point, Pressure Hold, Forward Flow, Water Intrusion) shall be correlated with microbial retention.

Vent Filters shall be integrity tested before and after use and shall be replaced based on the use period established during validation.

Automated Integrity Test Systems shall be validated.

Specifications shall be established for sterilizing filters and the filters Verified against these specifications prior to use. The verification shall be documented.

Third Party Validation Reports (e.g., Filter Manufacturer) shall not be accepted until an audit has been conducted that establishes acceptability of the validation program.

The Site Quality Team and the Site Production Team shall Approve and accept the audit report and assume responsibility for tracking any corrective actions.

A Contract with a Filter Manufacturer or Filter Supplier shall include a written agreement that no changes to the filter composition or configuration shall be made without first notifying the site purchaser(s). The Validation Committee (VC) shall determine Revalidation requirements for changes to the filter composition or configuration.

Process Stream Sterilizing Filters shall not be reused in a subsequent Campaign for an API or a subsequent lot for a drug product or medical device.

Good Working Practice – Manufacturing

Performance Qualification (PQ) for Filtration Systems used to sterilize APIs, drug products, medical devices, gases, and solvents shall include laboratory studies (e.g., filter manufacturer or in-house) to determine, at least, the following:

- Bioburden determination prior to sterile filtration for APIs, drug products, medical devices, and solvents;
- Microbial retention capability; and
- Verification of the filter manufacturer post-use integrity test correlates with total microbial retention.

Laboratory Microbial Challenge Studies shall be conducted for PQ and include:

- A minimum challenge level of 10^7 cfu per cm^2 of filter surface area of a challenge organism (e.g., *Brevundimonas diminuta*);
 - If the process stream is Bactericidal or Bacteriostatic for the challenge organism, the use of a product placebo or indirect challenge method shall be used and must ensure that the minimum challenge level is achieved; and
 - All of the Filtrate shall be captured and tested for total retention of the challenge organism. Pre-filtration Bioburden Specifications for APIs, drug products, medical devices, or solvents shall be established and/or confirmed during PQ, including:
 - Verification that the pre-filtration bioburden specifications are being met by sampling each batch/lot at the start, and again, just prior to the end of each filtration; and
 - Determination of such bioburden on a minimum of three (3) batches/lots.
- PQ for Compressed Gas Sterilizing Filters and Vent Filters shall include data from filter manufacturers that document, at least, the following:
- Microbial challenge studies; and
 - Correlation of the integrity test with total microbial retention.

Bioburden Levels prior to the sterilizing filter shall be monitored for every batch of liquid sterile drug product, and final phase aqueous sterile API and shall not exceed validated limits. If the bioburden levels exceed the validated limits, an investigation shall be conducted, which includes a documented risk assessment including at least the following:

- Identification of the microorganism(s),
- Assessment of bacterial endotoxin level, and
- Calculation of the total bioburden level for the lot/batch.

Filtration Time shall be monitored for each batch of liquid sterile drug product, and final phase aqueous sterile API to ensure that the validated maximum filtration time is not exceeded. If the validated maximum filtration time is exceeded, an investigation shall be performed to assess the impact on the product.

Integrity Testing conducted on a sterile filter, prior to use, shall be performed in a manner that prevents contamination of the sterile filter and sterile downstream equipment.

Integrity Testing of Liquid Process Filters shall be conducted within a validated time period after use to prevent a false integrity test result due to drying unless the filters are tested in place on the process equipment or the housings are sealed in a manner

Good Working Practice – Manufacturing

- Documentation of the number and location of thermocouples and BIs used during validation.

The Effects of Loading on Thermal Input to the Product shall be determined with minimum and maximum load configurations. Thermocouples shall be evenly distributed throughout the load in product containers as well as in the chamber. Documentation shall include, and not be limited to:

- High and low temperatures (range) during exposure;
- Come Up Time(range);
- Minimum and maximum product F_0 ;
- Exposure time (range);
- Come Down Time(range);
- Cooling cycle time (range);
- Product name, run date, and time;
- Any alarms that occur during the process; and
- Identification of the autoclave.

Sterilizer Monitoring and Control I/Es shall be calibrated before the Operational Qualification (OQ) study and routinely according to a defined calibration schedule.

External Monitoring and Recording I/Es (e.g., data logger and thermocouples) shall be calibrated before and after the OQ study and before and after the Performance Qualification (PQ) study.

Qualification Studies shall be performed for each product and each container or package size for moist heat terminal sterilization and shall include, and not be limited to:

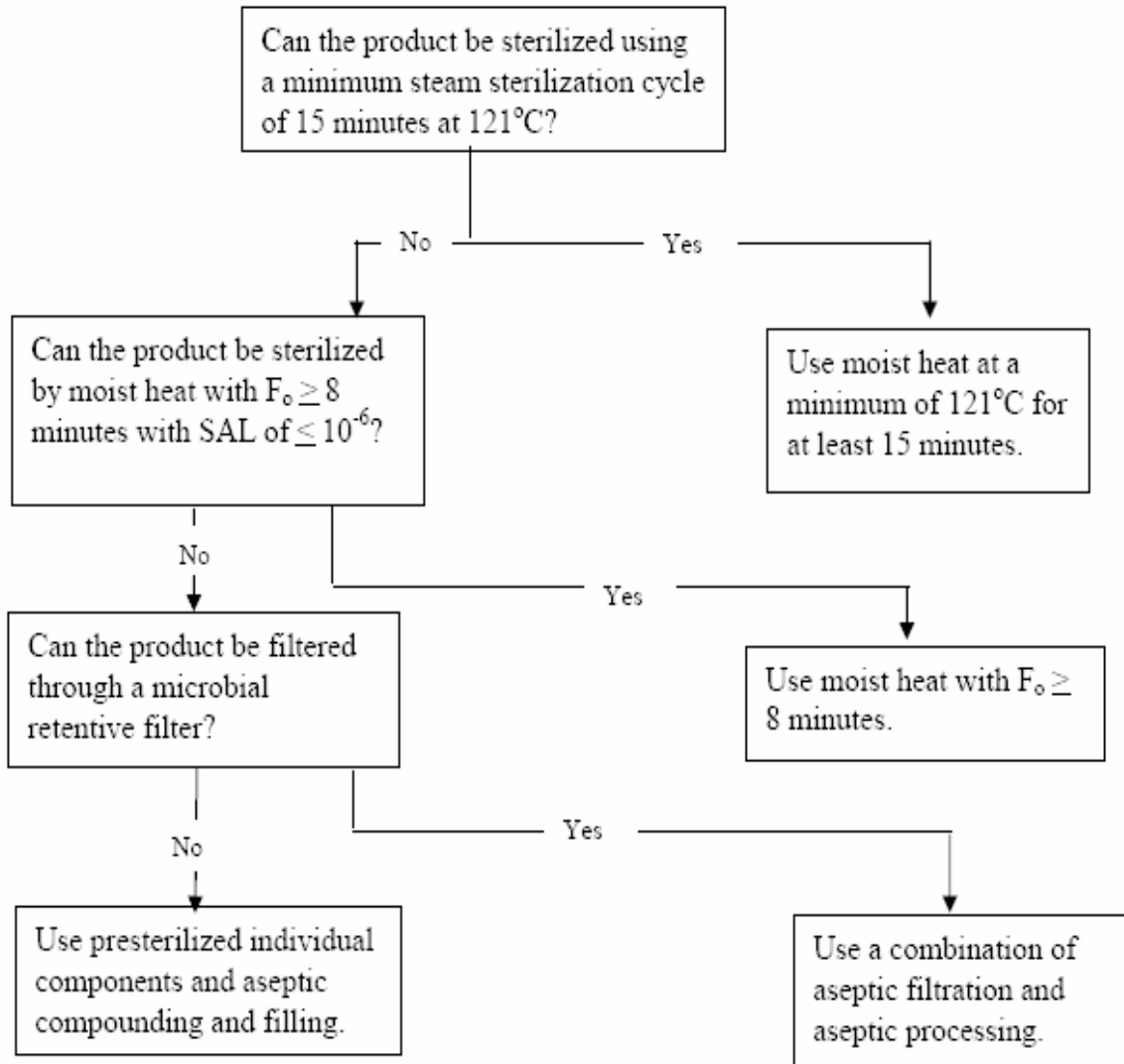
- Cycle using thermocouples in the chamber and in simulated or actual product;
- Verification of balance between internal head space pressure in the drug product container and the chamber pressure during all phases of the sterilization cycle to preserve container/closure integrity;
- Heat penetration studies for each different load configuration to confirm the Slowest-To-Heat Zone, and Worst Case load configuration;
- Verification that the stopper-cap interface is dry upon completion of the cycle;
- Verification of container/closure integrity before and after sterilization to ensure that the cycle does not cause container/closure integrity failure; and
- Verification of condensate control and removal from the sterilizer jacket, if present.

The Following Qualification Studies shall be performed initially and following significant changes (e.g., change to operating parameters, change to steam supply, change to controller, change to sterilizer location) for moist heat sterilization processes prior to production use:

- For a bracketing approach, a minimum of 3 consecutive, successful studies of each of the minimum and maximum load configurations (total of at least 6 studies) using minimum cycle set point parameters (e.g., sterilization temperature and/or time), BIs, and meeting all validation acceptance criteria; and

Good Working Practice – Manufacturing

Figure 1. Decision Tree for Sterilization of Aqueous Products (Ref 12)



Good Working Practice – Manufacturing

A Media Fill shall be invalidated when events unrelated to aseptic processing occur that impact the validity of the simulation. Media fills shall be declared invalid when any of the following conditions occur:

- Failure of the Growth Promotion Test;
- Incorrect incubation conditions; or
- Less than the required number of units is filled.

In the case of a culture medium growth promotion test failure, a media fill shall be declared invalid. The filling line can be used for production on a temporary basis, if the cause for the culture medium growth promotion test failure involves: laboratory testing error; media infertility caused by faulty preparation; or media infertility due to an incorrect ratio of sterile placebo material to liquid medium.

Initial Media Fills of each aseptic filling operation shall:

- Consist of a minimum of 3 consecutive, successful media fills;
- Be performed on 3 separate days and/or shifts;
- Be of sufficient duration to simulate all manipulations performed during actual operations; and
- Simulate the aseptic process from the point where the product is considered to be sterile for liquid products and from the point when product is added to the filler for powder filling.

The Media Fill Protocol shall address the following areas:

- Production instructions and Standard Operating Procedures (SOP) intended to be simulated;
- Maximum number of people in the APA, activities, changes, breaks;
- Complexity, aseptic manipulations, speed of filling operations, and Worst Case conditions;
- Maintenance of an event log;
- Duration of media fill;
- Number of units to be filled and incubated;
- Accountability for filled containers and rationale for Rejects;
- Routine and non-routine filling operation interruptions and interventions; and
- Environmental and personnel monitoring.

The Filling Room shall be cleared and cleaned between each media fill.

For Initial Media Fill Studies, if the filling line utilizes multiple vial types and line speeds, then a container configuration that includes a combination of all worst-case conditions with respect to size, fill, container neck opening, line speed, and manipulations, shall be used.

The justification for these configurations shall be documented for each filling line.

Re-qualification of Each Active Aseptic Filling Operation shall:

- Be performed twice a year at 5 to 7 month intervals on each shift;
- Use a container configuration supported by a justification;
- Consist of a single successful media fill; and

Good Working Practice – Manufacturing

- Sample containers shall be inoculated with the specified growth promotion organism(s) and incubated for 5 calendar days at the temperature range for the organism(s); and
- Growth in the positive control shall be confirmed as the Indicator Organism(i.e., Gram stain, genus or species identification).

A Batch Record or Device History Record (DHR) shall be completed for each media fill and shall include:

- Documentation normally included in a production filling record (e.g., container/closure sterilization data);
- Documentation of planned/unplanned interventions, including duration of intervention/stoppage, number of trays being filled, and time;
- Data regarding the filled and incubated units, including: # filled; # incubated; # of positive units; # of defective, rejected units for cause; and
- Results of growth promotion tests.

A Final Report on Each Media Fill shall be generated and shall include summary data from the event log, batch record or DHR, and environmental/personnel monitoring. The report shall document a conclusion regarding the acceptability of the media fill and shall be approved by the Validation Committee (VC).

Powder Media Fills shall include:

- Container filled with a sterile, microbiologically inert filling agent (e.g., polyethylene glycol 8000, lactose) to a level that is not inhibitory to microbial growth; and
- Units then filled with sterile liquid media (e.g., Soybean Casein Digest Broth), ensuring inert filling agent is in solution.

Media Fills Simulating Lyophilization shall include:

- A partial vacuum drawn on the lyophilization chamber that is held for a predetermined length of time at ambient temperature, after it is filled with media fill containers having unsealed stoppers;
- Release vacuum with sterile air and seat stoppers; and
- Crimp seal vials outside the lyophilizer after stoppers are seated.

In Small Scale Filling Operations (e.g., Clinical Supplies) where a batch size cannot be scaled to fill a minimum of 5000 vials, media fills shall be conducted in triplicate at the maximum scale possible for initial qualification. One media fill shall be performed for re-qualification. The acceptance criteria for each media fill shall be zero contaminated media fill units (see Fig 2).

Powder Media Fills shall include:

- Units filled with sterile liquid media (e.g., Soybean Casein Digest Broth); and
- Container then filled with a sterile, microbiologically inert filling agent (e.g., polyethylene glycol 8000, lactose) to a level that is not inhibitory to microbial growth, ensuring inert filling agent is in solution.

Good Working Practice – Manufacturing

batch number for that material. Blending of Multiple Lots (Batches) to make one lot (batch) shall be performed in a manner that ensures blend uniformity, and the new lot (batch) shall receive a new lot (batch) number.

When Different Portions of a Single Lot or Batch are subjected to individual processing such as in terminal Sterilization, Lyophilization or coating, each portion needs to be identified and tested, unless equivalency of the individual processing steps was demonstrated during

Process Validation. Traceability of an individual portion of the single lot has to be maintained until it is determined that the individual portion meets its specified requirements.

Palletized Glass Containers for Sterile Drug Products represent an exception to this Practice, since Labeling each container might jeopardize container cleanliness. An acceptable alternative is to label the shrink wrapping of at least eight modules (“bricks”) on the lowest layer of containers, so that two or more labels are displayed on each face of each pallet.

19. Aseptic Manufacturing Practices

Aseptic Manufacturing Practices shall be established for Aseptic Processing Areas (APA) used in the Production of Sterile Active Pharmaceutical Ingredients (API), sterile Drug Products, and aseptically processed Medical Devices, and shall include, and not be limited to, Standard Operating Procedures (SOP) and/or Specifications Approved by the Site Quality Team and Site Production Team for:

- Design of the facility and equipment;
- Facility and Equipment Qualification;
- Material and personnel flow;
- Contamination control;
- Sterilization of product and non-product items;
- Environmental monitoring;
- Validation of sterilization processes;
- Personnel training;
- Personnel health and hygiene;
- Preventive Maintenance (PM) and change control; and
- Validation of aseptic processing (e.g., Aseptic Processing Simulation).

This practice applies to the GMP sites where aseptic processing operations are performed.

APA Facility Design shall include, and not be limited to:

- Room and equipment layouts that minimize microbial and particulate contamination of products, including the use of Airlocks;
- Separate gowning and degowning rooms;
- Establishment of Air Classifications;

Good Working Practice – Manufacturing

- Opening or closing of sterile processing vessels or Containers;
- Sampling of sterile materials;
- Component additions to sterile vessels;
- Aseptic filling and stoppering of containers;
- Loading and unloading lyophilizers; and
- Sealing of ampoules.

Aseptic Connections and Manipulations shall be avoided whenever possible. If aseptic manipulations are required, only sterile tools (e.g., forceps) shall be used to handle sterile materials. These tools must remain sterile and, as necessary (e.g., when dropped on the floor or upon contact with non-sterile surfaces), be replaced during the operations. Tools shall be placed in sterilized containers between uses.

Aseptic Manufacturing Equipment and Processes used in the manufacture of sterile drug products, sterile APIs, and aseptically processed medical devices shall be qualified and validated using Protocols approved by the Validation Committee (VC):

- Sterile drug product aseptic processing shall be validated using aseptic processing simulation including filling and sealing operation; and
- Sterile API aseptic processing shall be validated by simulating aseptic operations.

Compounding/Storage Vessels that have been sterilized using SIP methods shall be maintained under positive pressure until use. Tanks shall be pressurized with sterile filtered air or nitrogen. Vessels must be drained of steam condensate and dried immediately after sterilization. The sterile hold times of these vessels must be qualified.

Tools Used in the APA (e.g., wrenches, screw drivers, forceps) shall be cleaned and sterilized prior to use. Instrumentation (e.g., Calibration standards) shall be cleaned and sterilized prior to use in the APA. Where sterilization is not possible, sanitization measures shall be used during entry into the APA through an airlock.

Materials shall be transferred into the APA through the APA airlock following a validated, sanitization process, for example:

- a) Materials are moved into the non-aseptic side of the APA airlock using a non-aseptic area transfer cart or skid;
- b) The materials on the non-aseptic area transfer cart are sanitized for a validated contact period;
- c) Gowned APA Personnel or APA Support Personnel enter the airlock from the APA and transfer materials to an APA dedicated cart in the airlock;
- d) APA Personnel or APA Support Personnel sanitize the materials and leave for a validated contact period on the cart or skid; and
- e) APA Personnel or APA Support Personnel move the materials on the APA dedicated cart into the APA.