Product Contact Equipment, both Major and Minor, used in production, Subdivision, or sampling of a drug product, In-Process Material, or Raw Material (RM) shall be cleaned and shall include, and not be limited to:

- Changeover Cleaning;
- Interval Cleaning during a Campaign, as necessary; or
- Dedicated Equipment Cleaning at the end of a campaign. Equipment disassembly may be required to clean or to Verify cleanliness.

Equipment Cleaning for major equipment must be conducted following written Instruction-Records or Standard Operating Procedures (SOP) with an attached checklist(s). These documents shall be Approved by the Site Production Team and Site Quality Team before being issued.

Equipment cleaning for minor equipment shall be conducted following written SOPs or Instructions-Records and these cleaning activities must be documented. The SOPs and Instruction-Records shall be approved by the Site Production Team and the Site Quality Team before being issued.

Executed Instruction-Records or checklist used shall be reviewed and approved by the Site Quality Team. Use and Cleaning History must be determined for product contact equipment that has been used by third parties or by another facility (e.g., trials, rentals, borrowed). The history must be documented and approved by the Site Quality Team. The removal of previous product residues must be verified, prior to any use.

The history shall demonstrate that the equipment was not used for and does not contain potential contamination from objectionable materials (e.g., penicillins or other beta lactams, pesticides).

Equipment Cleaning shall be designed to prevent Cross Contamination including microbiological contamination, when applicable [based on the Risk Assessment, by reducing residues on all product contact surfaces to acceptable levels. Maximum Allowable Residue (MAR) and Residue Acceptability Limit (RAL) for Equipment Cleaning shall be established by Qualified personnel based on the empirical data and the approved calculation method, prior to any use.

Swab or Rinsate Sampling Methods must be Validated through use of recovery studies. The Analytical Methods used to test for residue must also be validated. For Changeover Cleaning, Routine Verification of Cleaning Processes for Major Equipment Where One Hundred (100) Percent Visual Inspection is not Possible shall include:

- Inspection to the extent practical to verify the equipment is Visibly Clean;
- Periodic monitoring (e.g., using swab or rinsate sampling method as per validation) at a frequency defined based on a documented and approved risk assessment (e.g., up to 2 to 3 years) of the probability of contamination; and
- Approved justification of the rationale for the frequency of the periodic monitoring.

Routine Verification of Cleaning Processes for Major Equipment Where One Hundred (100) Percent Visual Inspection is Possible shall include inspection to verify the equipment is visibly clean (e.g., mills, filter housings, and tray driers).

After Completion of any Maintenance or Instrument Calibration Activities that required opening or disassembly of equipment, an evaluation must be conducted and documented to determine the level of cleaning required, if any, for product contact equipment.

Prior to Being Put into Service, New Equipment shall be cleaned and, the equipment shall be verified as visually clean at a minimum. The cleaning and verification of cleanliness must be documented and approved prior to use.

Equipment Cleaning Failures During Routine Monitoring (i.e., visual and/or analytical result failures) must be documented and Investigated according to established Site procedures. An evaluation of the impact on validation must be included.

2. Identification of Equipment Areas and Processes

Distinctive Equipment Identification Numbers or Codes shall be displayed clearly and prominently on all Areas and Major Equipment that involve, or are directly related to Production, and shall be used for referring to that equipment in all such documents as manufacturing, packaging, cleaning, and maintenance Instruction-Records, and in corresponding equipment logs and other similar records.

All Rooms and Areas Used for Production shall be identified at all times by function (e.g., filling room, blending room, packaging area, crystallizer room) and/or room number.

During Processing, Materials, Processing Vessels, Major Equipment, and Rooms that are involved in the process must be labeled or otherwise clearly identified (e.g., barcodes, Computerized Systems) with an indication of the product or material being processed including, and not limited to the following information:

- Name of the product or material being processed;
- Strength, if applicable;
- Batch Number or Lot Number;and
- Stage of production (e.g., crystallization, drying, blending, filling), when applicable.

Processing and/or Storage Vessels and their associated manifolds, filling, and discharge lines shall be identified in a manner designed to preclude incorrect use of the lines.

Fixed and/or Dedicated Processing Lines, Piping, and Other Conveying Devices that provide liquids or gases to production or control areas shall be clearly identified as to the contents and the direction of flow in a manner designed to preclude incorrect use of the lines.

- All identification from the prior product has been removed;
- The cleaning records are complete; and
- If applicable, analytical results are satisfactory.

For equipment cleaning procedures that require validation, the Site Quality Team must approve the executed cleaning records prior to the disposition of any batch of the next campaign.

- Maximum Allowable Time Intervals between use and initiation of cleaning shall be specified, unless there is an approved documented rationale or data demonstrating the time interval is non-critical. These intervals shall include consideration of the variables that could affect cleaning.

- After Completion of any Maintenance or Instrument Calibration Activities that required opening or disassembly of product contact equipment; an evaluation must be conducted and documented to determine the level of cleaning required, if any.

- Failures During Routine Monitoring (i.e., visual and/or analytical result failures) following changeover cleaning must be documented and Investigated according to established Site SOPs. An evaluation of the impact on validation must be included.

- Prior to Being Put into Service, New Major Product Contact Equipment shall be cleaned and verified as visually clean at a minimum. The cleaning and verification of cleanliness must be documented. All new product contact equipment (major and minor) must be visually inspected, if possible, prior to service to ensure that no debris or residue remains. Site Quality Team shall approve the approach to cleaning and verification of new major product contact equipment at the Site.

4. Calibration

This section of practice document establishes the requirements for the Calibration of equipment, instruments, and standards used in Production, storage and testing that may affect the identity, strength, quality, or purity of Pharmaceutical or Animal Health Drug Products, Active Pharmaceutical Ingredients (API),and Medical Devices.

This document applies to all GMP sites and operations and Logistics Centres responsible for production, control, and distribution of Pharmaceutical and Animal Health drug products, API and medical devices.

Calibration Program(s) shall be established and maintained in all gmp sites defining the responsibilities, criteria, and documentation requirements for the calibration of equipment and instruments used at that Site.

The Site Quality Team and the System Owner shall be notified of such events. The documentation shall include Impact Assessments on Batches or Lots produced using the system and associated components under investigation. The System Owner shall:

- Investigate additional PM work performed beyond that which is detailed on the individual PM instructions (i.e., PM Work Order);
- Initiate a deviation report if the investigation determines that there is potential impact to product quality; and
- Review and document the Verification that the PM was completed prior to returning the systems and associated components back into service. Defective Systems and Associated Components shall be removed from the location of use (e.g., Production Area), if possible, or at a minimum, designated as defective and out-of-service.

PM Records shall be current and readily retrievable and shall be maintained in accordance with the Site record retention SOPs.

Computerized Systems used to schedule or track PM, and/or to maintain PM records must be validated. Equipment Documentation (i.e., System Cleaning, Maintenance, and Use Records) resulting from PM shall be recorded.

PM Activities shall be performed and maintained by Qualified personnel. Records of training shall be maintained.

On-Site PM Performed by Qualified Contractors or Vendors shall comply with this document.

6. Cleaning and Sterilization of Aseptic Manufacturing Equipment

Equipment Used in Aseptic Processing shall be designed to minimize the risk of particulate and microbiological contamination. Design considerations for such equipment shall include, and are not limited to, the following:

- Sanitary fittings for all pipe and hose connections;
- Materials of construction that allow repeated cleaning and Disinfection treatments;
- Avoidance of crevices, occluded surfaces, and hard to clean areas;
- Product contact surfaces resistant to rusting, pitting, corrosion, and peeling; and
- Ease of assembly and disassembly.

This practice document applies to all GMP sites and operations where Sterile Active Pharmaceutical Ingredients (API), sterile Drug Products, and sterile Medical Devices are produced for Pharmaceutical and Animal Health.

Equipment Used in the Manufacture, Holding, Sampling, and Processing of sterile APIs, sterile drug products and aseptically processed sterile medical devices shall be cleaned and sterilized following written and Approved Standard Operating Procedures (SOP) and a Validated Process.

- Sterile Equipment shall be delivered to the Aseptic Processing Area (APA) in a manner designed to prevent contamination, such as through double-sided Batch sterilizers or Airlocks.

- The Maximum Time Interval Between Washing and Sterilization of equipment must be established and validated if the equipment is not stored under protected conditions. The maximum time interval between sterilization and use of equipment shall be validated.

- Measures to Differentiate sterile equipment from non-sterile equipment shall be defined. Examples of these measures include:
  - Supplier identification of sterile items;
  - Sterilization indicators;
  - Facility design (e.g., material flow patterns); and
  - SOPs for handling equipment before and after sterilization (e.g., material separation).

- Each Carrier (e.g., Cart, Basket, Tray, or Plastic Bag with Breather Panel) of Equipment and Individually Wrapped Equipment readied for sterilization shall be identified (e.g., with a non-shedding label such as Tyvek or metal tag) with the following information:
  - Identification of person preparing the equipment for sterilization;
  - Description of the equipment or item;
  - Sterilizer identification;
  - Specified sterilization cycle identification;
  - Date of sterilization; and
  - Expiration Date.
- Wrapped Equipment Sterilized in a Batch Sterilizer shall be unloaded and stored in an environment with the applicable air classification for a period of time not to exceed the maximum specified validated time interval.

- Sterilized Equipment shall be visually inspected for damage to the wrapping prior to storage or use. Damaged packages shall be labeled as damaged and removed from the APA.

- Equipment Cleaning and Sterilization shall be documented and included in batch /Lot Records.

7. Areas and Facilities Cleaning and Maintenance

- This section of practice document defines the cleaning and maintenance of GMP facilities (e.g., rooms/areas, modules) used in the Production, Sampling, or Subdivision of Drug Product Raw Materials (RM), Intermediates (post-introduction of the API Starting Material), drug product In-Process Materials, Active Pharmaceutical Ingredients (API), drug products, Packaging Materials, Biologics, or Medical Devices. Such areas or facilities shall be cleaned and maintained in ways that:
  - Ensure personnel safety;

8. Pest Control

This section of practice document defines the Pest control requirements for buildings and facilities at GMP sites and Logistics Centers that are used for Production, testing, or storage of the following:

- Raw Materials (RM),
- Starting Materials,
- In-Process Materials,
- Intermediates,
- Active Pharmaceutical Ingredients (API),
- Drug Products,
- Over-The-Counter (OTC) Products,
- Cosmetic products,
- Biologics,or
- Medical Devices.

- A Pest Control Program shall be implemented and maintained at each GMP Production Site and Logistic Center. The program must be designed to protect against entry and harboring of pests.

  Responsibility for maintaining the Pest Control Program shall be assigned to a Qualified Site Pest Control Coordinator.

- Pest Control Practices are to be described in current and available written procedures Approved by the Site Quality Team , including any Standard Operating Procedures (SOP) used at the Site by the contractor.

- Buildings and Premises shall be designed and maintained to protect against the entry and harboring of pests.

- Measures for Safe and Proper Use of Pest Control Chemicals shall be included in the Pest Control Program.

- Pest Control Chemicals shall be used only if the Site has written evidence that the chemicals are registered by government Team and used according to local, state, and national laws covering the use of pest control chemicals. The registration documentation for the pest control chemicals may be maintained at the pest control contractor location, but Site principals must assure that the documents exist before allowing the pest control contractor to use the chemicals at the Site.

- The Site Quality Team is responsible for approval of a Site-specific program for:
  - Inspection of rodent traps inside buildings used for production, testing, and/or storage and outside such buildings; and
  - Inspection, emptying and cleaning of bug lights.

- Pest Control Contractor Agreements must be in place at all Sites using pest control contractors.

chlorination, heat, ozonation) to provide microbial control. (Note: Deionized Water systems shall not be chlorinated as by definition the water would not meet the requirements for conductivity);
- Piping from water distribution systems to manifolds and process vessels shall provide drainage following use or shall be blown dry with filtered nitrogen or air;
- A bottom drain in storage tanks for drainage and cleaning;
- Air breaks in drain piping; and
- Positive pressure in distribution system.

- Storage and Distribution Systems for PW shall include:
  - Low carbon stainless steel (316L) or plastic storage vessels and piping;
  - Sanitary valves, pumps, and fittings;
  - Re-circulating distribution loops;
  - Means to minimize microbial contamination, such as Ultraviolet (UV) lights, heat treatment, or ozone injection;
  - Water return through a spray ball located in the storage tank headspace, except for systems that are ozonated or systems that are operated continuously hot;
  - A bottom drain in storage tanks for drainage and cleaning;
  - Vented tanks protected with Hydrophobic microbial-retentive filters designed to be condensate free (e.g., heated housings);
  - Tanks using a pressurized headspace in lieu of Vent Filters must be pressurized with a pharmaceutical grade gas (e.g., air or nitrogen) that has been filtered through a hydrophobic, microbial-retentive filter. Tank head pressure must be controlled;
  - Air breaks in drain piping; and
  - Positive pressure in distribution systems.

- In Addition to the PW System Design Requirements, Storage and Distribution Systems for HPW and WFI shall include:
  - Polished (e.g., 25 Ra micro inch or 0.64 Ra micron) or electropolished 316L stainless steel tank finish and sanitary piping with 3-A sanitary clamp-type fittings or equivalent; and
  - Double tube sheet heat exchangers and in addition, energy economizing heat exchangers meeting sanitary design standards that contain the same pharmaceutical grade water on both the utility and process sides of the heat exchanger may be used.

- Water Systems employing the use of ozone shall include inactivation of the ozone prior to using the water in manufacturing. Testing shall demonstrate that residual ozone levels are below established acceptable levels prior to use of the water system. Materials used in gaskets, in-line monitoring equipment, and sanitary valves shall be compatible with ozone when it is used in the water system.

Table 1: Water Use Requirements for Active Pharmaceutical Ingredients (APIs)

Water Types Permitted for APIs:[1]	Potable	Reduced Ion	Deionized (DI)	Low Microbial DI	Low Endotoxin DI	PW	HPW	WFI
Early & Intermediate Steps[2]	X	X	X	X	X	X	X	X
Final Steps[3] (Non-Sterile API):								
Type of Drug Product for which API will be used:								
• Non-Sterile Drug Product		X	X	X	X	X	X	X
• Non-Sterile Inhalation Drug Product				X	X		X	X
• Sterile, Non-Parenteral Drug Product				X	X		X	X
• Parenteral Drug Product					X		X	X
Final Steps (Sterile API):								
• Sterile, Non-Parenteral Drug Product						X[4]	X[4]	X[4]
• Parenteral								X[4]
Water Used for Cleaning/Rinsing of Equipment, Containers, Closures (Non-Sterile API):								
• Initial Rinse	X	X	X	X	X	X	X	X
• Final Rinse[5]	Same water quality as used in manufacturing of next product to contact equipment, containers, and/or closures.							
Water Used for Cleaning/Rinsing of Equipment, Containers, Closures (Sterile API):								
• Initial Rinse					X		X	X
• Final Rinse								X

Footnotes:

1. Water for production must be demonstrated to be suitable for its intended use.
2. Examples of water usage in early and intermediate API manufacturing steps:
   - Water is used to wash organic extracts;
   - Water or aqueous solution is used to quench a reaction upstream;
   - There are recrystallizations from the organic phase after the use of water;
   - There are chemical reactions after the use of water; and
   - Water functions as a Solvent* for strong base or acid.

(Table 1 footnotes continued on next page.)

(Footnotes Table 1: Continued from previous page)

3. Water used in final steps of API processes is defined as water that comes in direct contact with the isolated final API or the final solution prior to isolation of the API, or where the water is used as a final rinse on product-contact equipment, containers, or closures used for the final isolated API. Examples of water usage in final API manufacturing steps:
   - Later stages of API process for an API used in injectable or inhalation dosage forms;
   - If water is the last liquid to touch the API prior to drying (e.g., cake washing, precipitation, crystallization, or humidification for drying); and
   - API is precipitated or crystallized from solution by addition of water to an organic solution, with no subsequent dissolution of the solid, after isolation of the solid, even with organic cake wash.
4. Where no further sterilization steps are employed, the water must be rendered sterile.
5. If the water or solvent used for final rising during cleaning is lower quality than the quality required for the next process, the equipment must be rinsed with water or solvent at least as high quality as the water or solvent used for subsequent process prior to using the equipment.

- Air Handling Systems shall be Commissioned and/or Qualified appropriately.

- HVAC Systems for Aseptic Operations shall be designed with terminal High Efficiency Particulate Air (HEPA) Filters. Such HVAC systems shall be installed in a manner that allows for cleaning, maintenance, and control (e.g., air balancing dampers, control sensors) to be performed outside of APA with the following exceptions:
  - When self contained unidirectional airflow hoods exist and are needed within such areas;
  - When performing aerosol challenges and leak testing or replacement of individual HEPA filters with the area in a non-aseptic mode; and
  - When manual air damper controls are located in the area.

- HVAC Systems for Aseptic Operations shall be used to supply air under positive pressure to areas with following air classifications:

EU Grade	ISO Classification		US Designation	
	At Rest*	In Operation*	At Rest	In Operation
A	4.8	4.8	100	100
B	5	7	100	10,000
C	7	8	10,000	100,000
D	8	Undefined	100,000	Undefined

For Classification Purposes in Grade A Zones, a minimum sample volume of 1m^3 shall be taken per sample location. Sample volumes of less than 1m^3 are acceptable for routine monitoring.

- A Pressure Differential of at least 10 pascals [0.04 inches Water Gauge (WG)] shall be maintained between adjacent rooms of different air classifications, and shall be continuously monitored.

  A pressure differential of at least 12.5 pascals (0.05 inches WG) shall be maintained between the aseptic processing room and any adjacent unclassified room(s), and shall be continuously monitored.

- For Adjacent Rooms of the Same Air Classification that require a pressure differential to be maintained between the rooms (e.g., Lyophilizer filling area to lyophilizer loading area), a minimum pressure differential, sufficient to ensure airflow in the proper direction, shall be established during commissioning and/or qualification studies (e.g., Smoke Mapping Studies)and shall be monitored.

- For Products Requiring Special Containment Measures, such as live biological agents, cytotoxic drugs, sex hormones, and certain highly active drugs, additional measures must be in place to prevent Cross Contamination into

- Prefilter provisions;
- Airflow requirements;
- Efficiency rating;
- Materials of construction (Note: wood or wood components shall never be used);
- Gel seals or properly installed non-shedding gaskets (Note: asbestos gasket material shall never be used);
- Location and type of ports to permit in-place testing of static pressure and the introduction of aerosol challenge particles; and
- Manufacturer certification of filter integrity prior to shipment.

- Commissioning and/or Qualification of Air Handling Systems shall include but not be limited to, the following:
  - Perform HEPA filter Integrity Test;
  - Verify that the pressure drop across the HEPA filter meets manufacturer Specifications;
  - Conduct and videotape smoke mapping studies under "At Rest" and "In Operation" conditions using simulated operations in the vicinity of critical work areas and equipment;
  - Establish alert/action levels for airflow velocity at a defined distance proximal to the work surface (e.g., 6 to 12 inches above the work surface) for Grade A environments;
  - Identify and correct vortices or turbulent zones to ensure airflow is sweeping away from the work surface;
  - Confirm pressure differentials, humidity, and room air changes;
  - Establish recovery time to return to "At Rest" air classification specifications after operations or interruption to the air supply (e.g., power outage).
  - Measure total airborne particulate of the area laid out in a grid pattern, under "At Rest" and "In Operation" conditions;
  - Perform microbiological environmental monitoring under "At Rest" and "In Operation" conditions;
  - Analyze the data to confirm that the area meets the designated air classification; and
  - Select routine monitoring sites based upon the worst sites determined during commissioning and/or qualification.

Smoke Map Studies shall be visually recorded to a durable medium (e.g., videotape) and supported by a written narrative with specific conclusions. The written narrative shall be prepared following the execution of the smoke mapping studies and shall include the test data, notes, and conclusions. Voice over or other sounds are not required to be on the visual recording. The visual recording shall not be altered or edited, but the recording can be started and stopped as required during testing. The visual recording will serve as support to the written narrative. The visual recording shall be labeled with the Protocol number and title and protected to ensure it is "read-only." All observations made during the smoke mapping study of suspect equipment, personnel, or air pattern concerns shall be documented.

- An Acceptable Smoke Mapping Study shall meet the following minimum criteria:

Steam Distribution Systems, such as passivation chemicals, shall be Approved by the Site Quality Team. Testing and release requirements shall be defined by Specifications.

- The Equipment shall be Commissioned and/or Qualified and the process for preparing clean steam shall be validated.

- Clean Steam System Maintenance Measures shall include, at least, the following:

  - Maintain feedwater system in a state of control;
  - Monitor feedwater as Starting Materialfor clean steam;
  - Monitor and maintain, within specified ranges, clean steam pressure, temperature, and Conductivity; and
  - Preventive Maintenance (PM)for heat exchangers to assure integrity.

- A Documented and Approved Monitoring Program for clean steam shall be established and include, at least, the following:
  - Frequency of sampling and testing;
  - Minimum specifications for chemical and bacterial endotoxin quality of clean steam condensate meeting stated specifications for WFI;
  - Documentation and review of monitoring results, that include Trending;
  - Bacterial endotoxin Alert Level and Action Level limits; and
  - Documented Investigationsincluding corrective actions, when acceptable limits are exceeded.

- Steam Quality shall be tested at a frequency based on historical data, risk analysis, and local regulatory requirements.

- Clean Steam Condensate shall not be recovered for reuse in clean steam generation.

- Clean Steam Generators shall be designed to include, and not be limited to:
  - CalibratedI/E to monitor and record conductivity, temperature, and pressure;
  - Alarm and automatic shut off devices;
  - Properly designed double tube sheet heat exchangers to prevent Cross Contaminationfrom the plant steam to clean steam or its feedwater; and
  - Steam trap to vent condensate and non-condensible gases at the generator.
- Steam Traps shall be designed to:
  - Discharge condensate without leaking steam;
  - Discharge air and noncondensible gases from the system; and
  - Be resistant to blockage.

- Condensate Collection Systems shall be designed with atmospheric breaks to prevent back flow and contamination of the clean steam.

validated time intervals when not In Operation. Airlocks and gowning rooms shall be cleaned and disinfected, at least, daily when in use.

- Rubbish and Used Garment Bins shall be emptied on a daily basis or more frequently to avoid excess accumulation. Receptacles for discarded over wraps shall not be located within critical processing areas (e.g., Grade A), while the area is in operation.

- Floor Wax shall not be used in the APA.

- Vacuum Cleaners Used in the APA shall be dedicated to the area and have HEPA Filters on the exhaust. HEPA filter replacement frequency shall be justified and specified in written, approved procedures. HEPA filters installed in APA vacuum cleaners shall be Integrity Tested at installation and at least every 5-7 months thereafter. Vacuum cleaners shall not be used during aseptic processing.

- Only Materials, Equipment, or Tools that have been disinfected or Sterilized by a Validated Process shall be allowed in the APA.

- Sterilized Materials, Equipment, or Tools shall be used within a validated time period or else they shall be removed from the APA and resterilized or discarded.

- Equipment (e.g., mop heads, Sterilewipes) used to clean and disinfect in air classes Grades A to D shall be used in a manner designed to prevent Cross Contamination. Cleaning materials do not have to be sterilized for use in either Grade C or D areas. The need to sterilize cleaning equipment in a Grade C area depends on the intended use of the area. Methods for preventing contamination include, and are not limited to:
  - Mops shall have non-porous inorganic handles (e.g., stainless steel, plastic);
  - The mop head must be low particulate shedding (polyester, nylon or PVC), and compatible with the cleaning, disinfection, or sterilization process;
  - Mop heads, mop handles, and buckets shall be resistant to rust or corrosion caused by exposure to cleaning and/or disinfecting agents (e.g., hypochlorite);
  - Mop heads shall be discarded or cleaned and sterilized after each use. If mop heads are re-used, there must be an SOP that limits the number of times a specific mop head may be resterilized and re-used before it must be discarded;
  - Buckets shall be made of non-porous inorganic material (e.g., stainless steel, plastic) and shall be cleaned after each use and sterilized prior to use; and
  - Cleaning equipment shall be dry and stored in dedicated, well-ventilated storage cabinets or areas outside the APA.

- Sticky Mat Sheets Used at Entrances or Exits to the APA shall be replaced at least daily or more frequently if they become visibly soiled. Re-usable mats must be washed at least daily, and more frequent if they become visibly soiled.