Sterile & Non Sterile Manufacturing Operation Manuals

Manufacturing Documentation

Appropriate details of each process step must be described in chronological order and in sufficient detail to assure consistency from batch to batch. The equipment to be used must be identified and any necessary settings specified.

Appropriate environmental requirements for processing must be specified where necessary (e.g. temperature, humidity, air classification, etc). References to Standard Operating Procedures and check-lists must be given when applicable. Checks and double-checks to be made must be indicated, where these are required.

In-process controls, including alert/action/specification limits must be included. Any samples required must be included. Appropriate reconciliation checks and yield limits for major processing steps must be specified.

A statement of theoretical weight or measure for major processing steps must be included.

A statement of theoretical yield including the maximum and minimum percentages of theoretical yield must be included.

The identity of individual major equipment items and lines used must be identified.

Format and Layout:
Sufficient space should be provided where data are to be entered, e.g. starting and finishing times, material control numbers, equipment settings, process parameter, observations, calculations and confirming initials.

Space should be provided for documenting the name and batch number of the preceding product prepared in major pieces of equipment to be entered, and for documenting verification of equipment cleaning. Alternatively, this information can be recorded in equipment logs, providing that the retention and disposal of such logs satisfy the requirements given in Section 5.3 - Retention and Disposal.

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Maintenance and Calibration of GMP Critical Item

SOPs must exist which describe the overall calibration and maintenance program. Including:
- Identification of critical items requiring calibration and maintenance
- Establishing calibration and maintenance requirements and review during item lifecycle.
- Description of the workflow for calibration and maintenance.
- Management of ‘out of tolerance’ conditions and remedial actions
- Requirements for trend reviews (e.g. calibration failures, maintenance frequencies)
- Prevention from use of ‘un-calibrated’ and ‘out of service’ items
- Acceptance of items as suitable for use
- Use of contractor calibration and maintenance providers
- Documentation requirements
Calibration and maintenance activities are key components of the codes of good pharmaceutical manufacturing practice and therefore must be conducted by staff with appropriate training and will be the subject of self-inspection programs/audits, as defined in local procedures. Written procedures may also include details of how calibration and maintenance is conducted in support of other legislation such as Safety Health and Environment requirements.

**Critical items:**
Written procedures will describe the processes for review of inventory items (and their function) and agreeing which are critical and require calibration and maintenance. This must include review of an inventory of equipment that is prepared during initial qualification of a facility or laboratory as well as consideration of subsequent changes and additions to facilities, systems and laboratories.

The rationale used for classification of items as critical will be documented in local SOPs. A suitable rationale for declaring an item as critical is if it has the potential to:

- Affect the safety, quality or efficacy of a product
- Alter the physical, chemical or biological properties of a product,
- And/if testing/certification/maintenance is a local mandatory requirement (e.g. pressure vessel testing)

Alternative rationales for determining criticality, such the ‘direct impact’ approach described in the ISPE/GAMP Good Practice Guide: Calibration Management may also be acceptable.

**Retreatment and Blending of API & Formulated Product**

The re-treatment of products including rejected or sub-standard product should be by exception only. Where the batch integrity has been altered retreatment should not be carried out.

If retreatment is used for a majority of batches such processing should be included as part of the standard manufacturing process.

Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process and is not reprocessing.
Retreatment should only be allowed if the quality of the product will not be adversely affected by the retreatment, it is carried out in accordance with a defined procedure, and has been authorized by QA after evaluation of the risks involved, including any possible effect on product shelf life.

Proposals for retreatment of product manufactured at a contractor must be referred to the product Lead Site (site managing the contract or sponsor) for consideration and written approval prior to commencement of the retreatment activities.

The need for and extent of the validation requirements of all retreatment procedures should be carefully evaluated for each case of retreatment and approved by QA. All retreatment procedures that are intended to be a supplement to, or a part of the established manufacturing process should be validated by a prospective approach or at a minimum by a concurrent approach.

Retreatment should be carried out according to a written procedure and batch documentation should provide full traceability of all materials and operations performed.

Out of Specification batches must not be blended for the purpose of meeting specification.

Where blending is carried out blended batches must be traceable back to individual batches and the blend must be tested for conformance to specification and have expiry or retest life based on the oldest material used in the blend.

**In-Process Testing, Checks and Sampling**

In-process controls should have the ability to identify when corrective actions are needed and control the performance of processing steps that cause variability in the quality characteristics of products including intermediates and APIs.

In-process control activities should be based on the Master Formula or the Chemistry Manufacturing and Control (CMC) Documentation and on local process capability.

Written in-process control instructions must contain information about for example sample size, sampling frequency, test methods and locally established control limits. Samples must be representative of the batch.

When possible, established statistical techniques should be applied and where appropriate, the test methods validated.

The instructions for in-process controls could be given in Batch Records, procedures or in separate in-process control records. The records must have space for entering and signing test results. All raw data generated must be maintained with these records.

Qualified production department personnel can perform in-process controls. Sufficient space and qualified testing equipment should be available for the in-process controls.

Whilst normally in-process controls have associated control limits there may be occasions when additional testing is conducted to gather additional information and there are no control limits. If such testing is carried out it must be identified as ‘for information only’ and the purpose of gathering the data should be clearly understood.
stock. If a validated computerized storage system is used this segregation does not need to be physical, unless the returned goods falls under section 5.1.3. Where stock is returned from multiple sources, the stock from each source should be independently stored, i.e. the stocks should not be combined to form a batch.

**Receipt Handling and Storage of Starting & Packaging Materials**

Care must be taken that only one status is indicated on a container. This can be achieved by sticking the “Released” or “Rejected” label next to the “Quarantine” label, which should be crossed over. The labelling system should permit a check of identity on “Quarantine” label against the identity on “Released” or “Rejected” label to ensure that the right container is released or rejected. All labels should be stuck on the container body, not on the lid.

An individual assigned this responsibility and based on written instructions should perform the labelling operation. [Read Full Document www.gmpsop.com](http://www.gmpsop.com)

**Control of Packaging Operation**

The activities required to fill the bulk formulated product into primary containers and seal or fit closure. This includes addition of desiccants, wadding, etc., if contained within the sealed/closed primary pack.

In the case of sterile products, the primary packaging operation is carried out as an integral part of the manufacturing operation.

In the case of non-sterile products, the primary packing operation may be discontinuous with the manufacture of the bulk formulated product, and may be done in a different facility/site.

The primary packaging operation may include the addition/attachment of the legal labeling to the primary container.

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**Requirements for Facilities For Sterile and Non-sterile Drug Manufacture**

Sterile manufacturing must take place in clean areas. The areas should be classified in accordance with the regulatory requirements.

All areas must be built and validated to meet these requirements.

The particulate conditions for Grade A should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, for example due to the generation of particles and droplets from the product itself. There should be written justifications for any situation or process steps where this could apply.

The particulate conditions for the at rest state should normally be achieved in the unmanned state after a short clean up period of 15 - 20 minutes after completion of operations. This cleanup period should be validated and periodically monitored.

In some cases, the processing room and the adjacent clean rooms have the same classification. Maintaining a pressure differential between the processing rooms and the adjacent rooms can provide beneficial separation.

In order to reach Grade A, B and C the number of air changes should be related to the activity of the room.

Re-circulation of air within clean areas should not be practiced where the activities are creating dust. Re-circulation should preferably not be used to re-circulate air from areas where different products are handled. In cases where re-circulation is practiced the air should pass a filter system of an appropriate filter efficiency to minimize the potential for cross-contamination.

The following activities performed during sterile manufacturing must be conducted in area classified in accordance with the tables below.

**Labelling and Packaging of Investigational Medicinal Products and APIs in R&D**

There must be documented procedures to ensure that correct packaging materials and labels are used.

Label operations must be designed to prevent mix-ups. There must be physical or spatial separation from other unlabelled materials/batches.

Each container of isolated intermediate or API must be labelled as soon as possible during processing, with at least the following information:

- Batch number
- Product name/code
- Storage conditions, when such information is critical to ensure quality
- Material status (written or encrypted)

Note: Purchased API intermediates should be labelled to include the same information.

If the material is intended to be transferred outside the control of the site's material management system, the name and address of the manufacturing site, quantity of contents, special transportation requirements, if any, and any special legal requirements must be included on the label.
Intermediate or API containers that are transported outside of the site’s control must be sealed in a manner such that, if the seal is breached or missing, the recipient will be altered to the possibility that the contents may have been altered.

For material with expiration or retest dates, these must be included on the label and/or certificate of analysis.

Packaged or labelled materials must be examined to ensure that they have the correct label. This examination must be part of the packaging operation and documented in the production records.

Labelling for APIs intended for use in clinical trials should identify the material as being for investigational use. The “investigational use” label is not required for commercial API being used for clinical trials, or for investigational API stored within the own site, which is controlled through an electronic inventory system.

The applicable guidance given for IMP below should be applied for any pre-printed labeling used for API.

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**Principles and Responsibilities for the Management of Change in Operations**

All manufacturing sites shall establish a formal, documented system that evaluates the effectiveness of all changes proposed.

The impact of the change on the validation and registration status must be assessed. Risk management must be a part of this process.

The local QA unit must be involved in reviewing and approving all changes proposed.

The implementation procedure for all changes must ensure that regulatory and GMP compliance is maintained.

The operation of the system shall ensure adequate control and monitoring of change projects.

The system shall be designed to ensure the complete and accurate recording of the decisions to approve or reject a change and the history of the change from inception to implementation.

The system shall ensure that relevant documentation is updated accordingly.

All sites shall appoint a Site Change Manager with clearly defined roles and responsibilities.

All site should appoint a lead team which is responsible for the contractors are ensuring that appropriate links are established and maintained between the contractor and coordinated MCM process.

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**Alternatives Methods to Formaldehyde Fogging of Clean Rooms**

There are regulatory expectations for the periodic sanitization of clean rooms to ensure conformance to expected environmental bioburden levels though none of these explicitly require the use of fogging (2), (3), (4).
For biological facilities where viral contamination is a concern, there may be regulatory reasons to sanitize via fogging with some frequency as both Annex 2 of the European Commission and the World Health Organization’s GMPs for biological products mention the terms “shall” and “should” with regards to fumigation (4), (5).

Many non-biologics facilities successfully meet the general regulatory expectations for sanitization through the use of only liquid sanitizers, disinfectants, and sterilants. However, fogging can be very effective and may offer advantages over the use of liquid sanitizers in certain situations (e.g. very high ceilings, inaccessible surfaces that require sanitization, etc).

Fortunately there are other chemicals that can be used to fog clean rooms. Although there are others, three potential replacement options are listed below along with some advantages and disadvantages of each. It should be noted that what is considered an advantage is highly dependent on the specific application. These chemicals are all considered sterilants under certain conditions though the concentration of the agent that is required to achieve destruction of bacterial endospores varies greatly. With proper design and validation, all can have good distribution throughout the clean room on a consistent basis. Labor costs are still typically lower than with liquid sanitizers because the chemical can be distributed by airflow instead of by personnel.

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**Cleaning and Sterilization Practice of Aseptic Manufacturing Equipment**

Preventive Maintenance of CIP/SIP Systems should include, and not be limited to, the following:

- Calibration of Instruments and Elements (I/Es);
- Verification of cycle parameters (e.g., length of each cycle, amount of CIP chemicals used during the various cycles, pH);

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• Inspection of the CIP/SIP system for rusting, pitting, or corrosion; and Passivation, as required.

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**Sterile Product-Package and Container Integrity Testing**

Challenged Containers that Show Microbial Growth Upon Microbial Ingress Testing should be inspected to determine whether defects in the container closure seal permitted microbial ingress. All defects observed should be described and documented. An investigation should be conducted to determine the cause of the contamination, including a comparison of the contaminant organism(s) to the challenge organism.

Non-Microbial Methods for Container Closure Integrity Testing should be based on validated studies that correlate the test method to microbial ingress testing. Non-microbial integrity tests should be used during routine processing, at a minimum:

• During equipment set-up;
• As an In-Process Control (IPC) test;
• On representative samples of the finished batch/lot; and
• On stability samples during the shelf life and at lot expiration date.

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**Microbial Bioburden and Quality Control of Oral Solid Dosage Forms in Pharmaceuticals**

The most common microbial hazards that can jeopardize product quality of solid oral dosage forms can often be attributed to contaminated raw materials. Microbial hazards may be introduced into a manufacturing process due to the improper sanitary design of the manufacturing equipment; especially equipment used for aqueous processing steps (i.e., wet granulation or tablet coating).

For example, microbial contamination can arise from entrapped water or product residues that remain hidden from procedural cleaning processes due to threaded pipe fittings, non-sanitary valves, piping dead legs, non-sloping pipes, equipment crevices, recessed access ports, bottom discharge valves, and pocket flow meters. Inadequate equipment maintenance may also serve as a potential microbial hazard. For example, misaligned, damaged, or over torqued gaskets between piping connections may harbor a reservoir of trapped microorganisms.

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**Defining and Equating Worst Case Conditions for Aseptic Process Simulations**

First it is important to note that the definition of “worst case” does not mean execution of a media fill at processing failure points where media fill failure would likely occur. Instead, it is the expectation that “worst-case” conditions within the media fill are designed to be performed at the normal operating limits of the production process. Also, “worst-case” conditions should be considered and defined within the media fill simulation program for product holding times, process filling times, filling line speed, container sizes, interventions and personnel.

Members within the regulatory community agree that “media fill studies should closely simulate aseptic manufacturing operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations”. Practical ways to help determine appropriate process
“worst-case” conditions include reviewing routine production batch records as well as observations performed as part of routine aseptic manufacturing operations.

A preferred “worst-case” application would be to hold the bulk for a time that just exceeds the maximum time for holding product during routine manufacturing operations. The holding time simulation for holding vessels containing sterilized product “should be covered by a process simulation test on a regular basis unless a validated, pressure hold or vacuum hold test is routinely performed”.

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How Does Gamma Radiation Sterilization Works

Establishment of a Sterilization Dose Using AAMI Method 1 for a Single Production Batch includes the following steps:

   a. Determine the average indigenous bioburden of the API, drug product, medical device, or non-product item using ten (10) randomly collected samples;
   b. Determine the verification dose for a Sterility Assurance Level (SAL) of 10-2 from an AAMI table using the average bioburden (see ANSI/AAMI/ISO 11137-2:2006);
   c. Verify that the verification dose does not exceed the established maximum sterilization dose limit;
   d. Irradiate one hundred (100) samples of the product batch at the verification dose;
   e. Perform a sterility test on each of the one hundred (100) samples
   f. If there are no more than two (2) samples with positive sterility tests, then accept the verification dose; and
   g. Using the AAMI table, determine the sterilization dose for the required SAL (e.g., 10-6) based on the average bioburden for the batch.

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Bottle Filling at Pharmaceuticals Production
Good Practices of Loading and Unloading Multiple Lyophilizers From a Common Corridor

The FDA, in its Guidance for Industry: Sterile Products Produced by Aseptic Processing – Current Good Manufacturing Practice requires that “... partially closed sterile product should be transferred only in critical areas. Facility design should ensure that the area between a filling line and the lyophilizer provide for Class 100 (ISO 5) protection. Transport and loading procedures should afford the same protection.”

The FDA set similar requirements in their earlier Guide for Inspection of Lyophilization of Parenterals. Here, FDA stated “The transfer and handling, such as loading of the lyophilizer, should take place under primary barriers, such as the laminar flow hoods under which the vials were filled. Validation of this handling should also include the use of media fills.”

The EC also requires that “Prior to completion of stoppering, transfer of partially closed containers, as used in freeze drying should be done either in a grade A environment with a grade B background or in sealed transfer trays in a grade B environment.

No requirements are stated for unloading the dryers. Here, with internal stoppering, the stoppers have been fully seated within the protection of the closed dryer. No requirements are stated for separation (in time or space) of loading and unloading activities or between multiple dryers.

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Trending of Environmental Monitoring and Preventative Actions

When Environmental Monitoring data is analyzed with appropriate statistical and qualitative techniques, knowledge of the environment becomes more significant and decisions based on this knowledge easier to defend. The easiest form of trending is to consider a certain number of alert level excursions equivalent to an action level excursion. This type of trending is good for quickly spotting an adverse situation over a relatively short timeframe (e.g. weekly trending).

Commonly, three alert level excursions in ten consecutive samples are sufficient to initiate an investigation. However, the nature of the operations conducted at the particular monitoring point should be considered when deciding on a number.

This approach can be applied to a single sampling point, or more conservatively, to an entire air classification within a production suite. While alert level excursions will show adverse trends in the short term, more advanced statistical treatment is required for longer-term data analysis.

When deciding on a statistical tool for use with Environmental Monitoring trending, it is important to keep two things in mind. First, make sure the statistical tools are appropriate for their intended use.

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Integrity Assurance of Packaging Materials for Sterile Drug Product and Medical Devices

In-Process Controls used to verify packaging system integrity include and are not limited to, the following:

- Torque monitors for screw-capping equipment;
- Headspace analysis for products requiring inert gas headspace; and
- Visual inspection of seals.

In-Process Control Sampling and Test Procedures should include and not be limited to:
• Number of samples to be tested per batch/lot;
• Test Methods (TM);
• Test equipment;
• Acceptance criteria; and
• Retest criteria and methods.

Effective Control & Prevention of Cross Contamination in Pharmaceutical Manufacturing

Precautions should be established and maintained to ensure that cross contamination at product exposure points (e.g., open hatch charging or sampling, packout, heel scraping) is prevented from overhead equipment and piping. Consideration should be given to such precautions, including, and are not limited to, the following items:

• Booth or canopy over tank hatch openings;
• Isolators (e.g., glove boxes);
• SOPs defining conditions under which vessels can be opened;
• Periodic inspection of overhead piping and ducts to ensure that there are no leaks, condensation, flaking of paint and/or insulation that might fall into vessel openings;
• Drip pans under HVAC units or cold surfaces to collect or contain condensation; and
• Facilities designed with minimal overhead ducts and piping.

Effective Control & Prevention of Fungal Contamination in Tablets Containing Drug Products

The microbial quality of the raw materials and APIs directly impact the microbial quality of the final tablet product. Fungal populations that may be found in these raw materials can contaminate the final tablet product. This is because the manufacturing of most tablets does not include processing steps that can eliminate the indigenous bioburden found originally in the raw material.

Based on the materials contribution to the final drug product and their ability to be validated for their microbial attributes, it may be necessary to test RMs and API on a routine or periodic basis.

Therefore, it is recommended that raw materials and API's used in the manufacturing of the tablet be evaluated for their contribution to Total Yeast and Molds in tablets. This includes the testing of APIs that are manufactured and/or milled at one site (internal or external) and then transferred to the tablet-manufacturing site.
Managing Rotation of Sanitants in a Routine Sanitization Program

Of primary importance in any sanitization program is the proper selection of a chemical agent to reduce microbial bioburden. Selection should be based upon the number and specific microorganisms present in the area where the sanitizing agent is to be routinely applied.

In addition, effective cleaning should precede any application of sanitant. The condition of the surfaces that are to be sanitized require proper conditioning through cleaning, since deposits can prevent proper sanitizer contact with target microorganisms. Furthermore, residues on the surface to be sanitized have been found to inactivate or reduce the effectiveness of some types of sanitizers (e.g. hypochlorites) rendering the sanitization procedure ineffective”.

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Validating Sterilization and Depyrogenation of Pharmaceutical Direct Contact Equipments

For Steam Sterilization Processes, biological indicators are available in four (4) forms:

- Spores added to a carrier (e.g., a disk or strip of filter paper, glass, plastic or other material) and packaged to maintain the integrity and viability of the inoculated carrier (preferred and most commonly used in non-product sterilization validation);
- Self-contained packaged indicator that includes the culture medium separated from the biological indicators (e.g., a paper strip surrounding a sealed ampoule containing culture medium that is activated after exposure);
- Self-contained packaged indicator that includes the spores suspended in the culture medium in a sealed ampoule (most often used for submersion in liquids); and
- Spore suspension added to representative units of the product, simulated product, or onto non-product surfaces (e.g., closures). Such suspensions are most often used for product terminal sterilization validation.

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Managing Unplanned Power Outage Time Limit and Recovery Within the Clean room Area

Determination of a time limit consists of extensive environmental monitoring after the APA power has been interrupted and the critical air handling systems ceases to function. This may also includes interruptions to the air handling systems of areas adjacent to the APA that would be affected by the interruption.

The essential monitors to include in the determination are total airborne non-viable particulates, viable quantitative (active) air and/or viable passive air (settlement plates), and pressure differentials. Additional parameters such as temperature and humidity should be tested if they are critical to the process.

The Non-viable monitors and pressure differential monitors are the most sensitive indicators for detecting any changes in the quality of the APA environment. The state of microbiological control in an APA can be directly correlated from these monitors.

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Management of Sterilized Goggles Within the Aseptic (Clean Room) Processing Area

Goggles can be obtained sterile and ready-to-use as disposable or re-sterilizable models. Sources have been identified that can supply sterilized goggles to virtually any part of the world.

While disposable goggles may be more costly and generate excess waste, this practice eliminates the need for tracking the sterilization history of the goggles and verification or maintenance of a cleaning and re-sterilization program. At least two disposable models are available. These goggles are available triple wrapped, sterilized by ethylene oxide or gamma irradiation. Validation documentation of the sterilization of these goggles needs to be reviewed and is available from certified vendors.

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Management of Non-Sterile Active Pharmaceutical Ingredient (API) Manufacturing Area

The risk assessment may be conducted on a product or facility-centric basis. This risk assessment should include consideration of at least the following:

- Type of API manufactured (e.g., small molecule API via chemical synthesis or classical fermentation);

- For APIs produced by chemical synthesis or classical fermentation, the risk assessment should be conducted to include the step where the API molecule is formed and on each of the subsequent step(s) of manufacture, including an evaluation on whether or not there is further purification of the API;

- For APIs exposed to the environment, the subsequent Drug Product dosage form (e.g. oral, parenteral, topical, inhalant) should be considered during the risk assessment. For APIs subsequently used in multiple dosage forms, it is recommended that the most conservative dosage form with respect to patient safety (e.g., parenteral) is considered in the risk assessment;

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**Water Activity Fundamentals and Applications in Pharmaceutical Operations**

Water activity is defined as the ratio of product vapour pressure to pure water vapour pressure. It is a measure of the water available for chemical or microbiological activity within a product. It is not a measure of the total water content of an item, as water can be chemically bound and not be available for use. Its values are typically expressed as a decimal value and can range from 0.0 (completely dry) up to 1.0 (pure water).

Though the principles of water activity have been used for centuries (e.g. salting, drying, mummification), its use by the FDA occurred in the 1980’s when water activity testing was added to existing strategies for microbiological control in food products.

Water activity is significant to the pharmaceutical industry in that it affects the quality of ingredients and finished product through their chemical stability, a reduced need for chemical preservatives, and a potential reduction in the need for microbial limits testing.

Microbial growth requires water. Water dissolves solutes within a viable cell and is required for metabolic function. When an water activity value is associated with a micro-organism it serves as an indication of potential metabolic activity. While organism proliferation ceases below certain water activity levels, some species have the ability to adapt slightly and continue to grow at levels below their optimum range.

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**Container / Closure & Environmental Assessment Drug Products of Shipping Processes**

A documented risk assessment (for more robust products) or risk assessment plus completed shipping quality study (for more sensitive products) will provide scientifically-based justification that the risks have been considered and that, when warranted, risks posed from shipping the drug products have been appropriately mitigated. An additional benefit provided by this documented information is that local receipt testing of the drug products by the receiving site, should not be necessary from a quality control or quality assurance perspective.

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Cold Chain Management Practice for Bio and Pharmaceutical Materials

Biopharmaceuticals products are generally derived from living material: human, animal or microorganisms, are complex in structure, and are usually not fully characterized. Many forms of the same molecule collectively define the drug “heterogeneity profile”.

Unlike small molecular weight drugs, which have a well-defined structure and consistent purity, biopharmaceuticals are of large molecular size and structural complexity, and display consistent heterogeneity. Traditional small molecule drug products usually consist of pure chemical substances that are easily analysed after manufacture.

Biopharmaceutical products are often defined by their manufacturing processes. Changes in the manufacturing process, equipment or facilities could result in changes to the biological product itself and potentially require additional clinical studies to demonstrate the product's safety, identity, purity and potency.

Biopharmaceuticals are further characterized by their high susceptibility to irreversible degradation and exceptionally high financial value per unit. Temperature, agitation and exposure to light are among the conditions known to degrade protein and oligonucleotide based materials.

A risk assessment should be conducted that examine potential conditions under which the integrity of each biopharmaceutical materials is known to be compromised. Among the points to consider: temperature, Exposure to CO$_2$, Agitation/Vibration, Pressure Cycles etc.

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Clean Process Vial Capping Operations in Pharmaceuticals

The routine monitoring program may be designed to monitor both the physical parameters of the air handler and empirical data (i.e. non-viable particulates) in order to provide information on the air source to the capping operation since this ensures that the monitoring is focused on verification of air quality being supplied to the capping process versus the process itself.

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Recovered and Recycled Solvents from the Active Pharmaceutical Ingredients Manufacturing

Validated Solvent Recovery Processes that undergo major changes to incoming used solvent streams (e.g., those requiring a new solvent recovery process, or a stream that does not fit established criteria) require revalidation. In addition, major changes to equipment, facility, procedures or the solvent recovery process may require revalidation. Minor changes may not require revalidation but may require a documented, expanded test program or other formal evaluation.

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Metal Detection Systems for Pharmaceuticals Preparation

All Metal Detectors used in Manufacturing Operations (including, but not limited to, encapsulation and tabletting) should be qualified and subsequently set-up and operated such that the detectors will, 100 percent of the time, detect and isolate spherical 0.5mm ferrous, spherical 0.5mm non-ferrous, and spherical 0.8mm stainless steel metal embedded in discs or cylinder carriers that are used to challenge the system.

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All Metal Detectors used in Packaging Operations should be qualified and subsequently set-up and operated such that the detectors will, 100 percent of the time, detect and isolate spherical 1.0mm ferrous, spherical 1.0mm non-ferrous, and spherical 1.5mm stainless steel metal embedded in discs or cylinder carriers that are used to challenge the system.

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Storage, Handling, Cleaning and Maintenance of Hose in Pharmaceuticals

GMP sites should have procedures defining the use, specification, storage, handling, cleaning and maintenance of hoses used in cleaning and production of intermediates and APIs in accordance with cGMP guidelines. Flexible hoses should be adequately identified, maintained, and cleaned.

Section 5.2 - Q7A, emphasizes written procedures should be established for cleaning equipment and its subsequent release for use in manufacture of intermediates and APIs. In addition, sites should have standardized hose management practices, including management of change, with written procedures that identify factors to be considered and evaluated.

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