

Title: Good Working Practice – Validation Requirements					
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Topics:

1. **Biological Test Methods Validation**
2. **Analytical Methods Validation**
3. **Equipment Cleaning Validation for Active Pharmaceutical Ingredients (APIs)**
4. **Equipment Cleaning Validation for Drug Products**
5. **Laboratory Equipment Qualification**
6. **Microbiological Methods Validation**
7. **Packaging Validation**
8. **Process Validation for Active Pharmaceutical Ingredients (API)**
9. **Process Validation for Drug Products and Medical Devices**
10. **System Validation**
11. **Validating Aseptic Processing - Active Pharmaceutical Ingredients (API)**
12. **Validation of Analytical Methods for Equipment Cleaning**
13. **Validation Requirements and Documentation**

- Precision,
 - Repeatability,
 - Intermediate Precision (intra-laboratory), and
 - Reproducibility (inter-laboratory),
- Specificity, and
- Quantitation Limit (QL).

Robustness of the biological test method shall be considered during method validation if not addressed during method development.

Validated alternate biological test methods shall be submitted to the Regulatory Authority, when required, prior to implementation.

Biological Test Method Validation or Verification Studies shall be performed and documented according to an Approved Protocol that defines the parameters being evaluated, the acceptance criteria for each parameter and the Test Methods. The protocol must be approved by the Laboratory Manager prior to execution of the validation studies.

A Method Validation or Verification Report shall be prepared that documents the results of the validation or verification study, including the evaluation of each parameter and comparison against acceptance criteria. Any Deviations from the protocol must be documented and the impact of the deviations discussed in the report.

Qualified Personnel shall be identified with the following roles and responsibilities in regards to biological test method validation or verification:

- The Laboratory Manager at the Site conducting the validation or verification is responsible for assuring that the biological methods are validated or verified and for reviewing and approving the Final Report; and
- The Quality Authority, independent of the Laboratory Manager, at the Site conducting the validation or verification study is responsible for reviewing and approving the final report for compliance with applicable Site policies and procedures.

Automated Systems used as a part of a biological test method and Computerized Laboratory Systems shall include Validation of the computerized system. Qualified Personnel shall perform:

- Validation studies, and
- Verification of compendial methods.

Written and Approved Procedures shall describe the preparation, Laboratory labelling, storage, and use of laboratory Reagents, solutions, buffers and Reference Standards.

Test Equipment used in the execution of the biological test method protocol must be qualified and have a current Calibration status.

- Quantitative tests of the active moiety in samples of API, drug product, medical devices, or dissolution samples; and
- Quantitative tests on drug product for other selected component(s) in the drug product.

This guidance also applies to methods used to evaluate physical properties (e.g., particle size). This guidance does not apply to the validation of microbiological or bioanalytical methods or Test Methods (TM) associated with Equipment Cleaning Validation.

Analytical Method Validation shall include consideration of the following validation characteristics:

- Accuracy,
- Precision,
 - Repeatability,
 - Intermediate Precision (intra-laboratory), and
 - Reproducibility (inter-laboratory),
- Specificity,
- Detection Limit (DL),
- Quantitation Limit (QL),
- Linearity,
- Range, and
- Robustness.

Notes:

Data for one characterization may be used to meet the requirements of another characterization. Robustness of the method shall be considered during method validation if not addressed during method development.

Reproducibility is not required for method validation. However, reproducibility may be used in place of intermediate precision.

Typical validation characteristics applicable to different types of methods (e.g., limits, identification, quantification) are presented in Tables 1 and 2. For test methods used to evaluate physical properties, intermediate precision shall be considered, at a minimum.

- System Suitability -depending on the nature of the analytical method, a set of criteria shall be established during development or validation to verify performance of the analytical method or system.
- Validation Documentation and Records for Method Validation shall meet requirements set out in respective guidance for validation documentation.
- The Method Validation Protocol must document the validation parameters being evaluated, the acceptance criteria for each parameter, and the test method(s). The protocol must be Approved by the Lab Manager prior to execution of the validation studies.

Critical separations in chromatography shall be evaluated for the active ingredient at the concentration specified in the analytical method and for impurity(s) at Specification level(s), when possible.

Specificity can be demonstrated by the resolution of the two components that elute closest to each other.

- If Impurities or Degradation Products Are Available, the API, drug product or medical device shall be spiked with impurities to demonstrate the specificity of the analytical method.

For assays, specificity is established by demonstrating that the analytical response of the analyte of interest is unaffected by the presence of other components in the sample. For an impurity test, specificity is established by demonstrating that the impurities are separated from each other and/or from other components in the sample matrix.

- If Impurities or Degradation Products Are Not Available for use in demonstrating specificity then samples that are known to contain the impurities and/or degradation products will be used to demonstrate specificity, when available.

For stability indicating methods, such demonstration shall include drug product, API, or medical device samples stored under relevant stress conditions (e.g., light, heat, humidity, acid/base hydrolysis, and oxidation). In cases where degradation pathways have been established, degradation products have been identified, and authentic substances are available there is no need to perform forced degradation.

Alternatively, specificity is demonstrated by comparing the test results of samples containing impurities or degradation products to a second well-characterized method [e.g., compendial method or other validated analytical method (independent procedure)].

For the assay, the two results shall be compared; and for the impurity tests, the impurity profiles shall be compared.

If samples containing the impurities and/or degradation products are not available, chromatographic peak purity assessment (e.g., diode array or mass spectrometry detection) may be useful to show that the analyte chromatographic peak is not attributable to more than one component.

- Analytical method for quantitative impurity and assay methods (including methods for dissolution and Content Uniformity). It shall be demonstrated directly on the analyte and/or with mixtures of the analyte and sample matrix using the proposed analytical method.

Linearity shall be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. If there is a linear relationship, test results shall

purity are performed together as one test and only a single standard is used, linearity, accuracy and precision must be demonstrated from the reporting level of the impurities to 120 percent of the assay specification.

- Accuracy shall be established across the specified range of the analytical method. This applies to assay methods, including methods for dissolution and content uniformity, and to quantitative impurity methods for API, drug product and medical device.
- The Accuracy of API Assays shall be demonstrated by one of the following methods:
 - a) Application of the analytical method to an analyte of known purity (e.g., reference material);
 - b) Comparison of the results of the proposed analytical method with those of a second well-characterized method, the accuracy of which is stated and/or defined; or
 - c) Accuracy may be inferred once precision, linearity, and specificity have been established.
- The Accuracy of Drug Product Assays shall be demonstrated by one of the following:
 - a) Application of the analytical procedure to placebo mixtures of the drug product components to which known quantities of the API to be analyzed have been added; or
 - b) In cases where it is impossible to obtain samples of all drug product components, it is acceptable either to add known quantities of the analyte to the drug product or to compare the results obtained from a second, well characterized method, the accuracy of which is stated and/or defined.
- Impurities (Quantitation) - accuracy shall be assessed on samples (API or drug product) spiked with known amounts of impurities. In cases where it is impossible to obtain samples of certain impurities and/or degradation products, it is considered acceptable to compare results obtained by an independent procedure.

The response factor of the API can be used to quantitate the impurities and/or degradation products. Alternatively a surrogate (e.g., compound whose structure and properties are closely related to the impurity of interest) may be used to demonstrate accuracy.

For API and drug product quantitative impurity methods, accuracy may be inferred when the acceptance criteria for specificity, linearity and precision are met.

- Accuracy: If determination of accuracy is required (i.e., not inferred), the following accuracy requirements shall apply. For assay methods (including methods for dissolution and content uniformity), and quantitative impurity methods for APIs and drug products, accuracy shall be assessed using a minimum of nine (9) determinations over a minimum of three (3) concentration levels covering the specified range of the analytical method [e.g., three (3) concentrations with three (3) replicate sample preparations each].

- Quantitation Limit (QL) is established for quantitative tests for impurities. The QL and the method used for determining the QL shall be presented in the validation report. The QL shall be validated by the analysis of a minimum of three (3) samples known to be near or prepared at the QL and demonstrating accuracy and precision. At a minimum, the QL shall be at or below the reporting limit for the compound under test.
- Robustness shall be considered during either the method development phase or validation and depends on the type of procedure under study. Robustness shall demonstrate the reliability of an analysis with respect to deliberate variations in method parameters. If measurements are susceptible to variations in analytical conditions, the analytical conditions must be controlled or a precautionary statement included in the procedure.

Data collected during robustness studies shall be used to set or verify system suitability requirements.

- System Suitability Test Parameters to be established for a particular method depend on the type of method being validated.

Typical system suitability parameters for chromatographic systems to consider during validation are:

- Peak resolution (R) of the peaks of interest and/or other components;
- The RSD of replicate injections for precision (repeatability);
- The tailing factor (T) for peak asymmetry; and
- The Sensitivity check
 - A Sensitivity Test Solution is used, or alternatively,
 - Column efficiency.

Table 2. Analytical Methods Validation Characteristics Applied to Different Types of Analytical Methods for Active Pharmaceutical Ingredients, Drug Products, and Medical Devices

Characteristic	Identification	Testing for Impurities		Assay, Dissolution (measurement only), Content/Potency
		Quantitation	Limit Test	
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Intermediate Precision	-	+(b)	-	+(b)
Reproducibility	-	+(b)	-	+(b)
Specificity	+	+	+	+
Detection Limit	-	-	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+
Robustness	(a)	+	(a)	+

Key:

+ Signifies that this characteristic is normally evaluated.

- Signifies that this characteristic is not normally evaluated.

(a) To be considered if critical to the method; and

(b) In cases where reproducibility has been performed, intermediate precision is not needed.

3. Equipment Cleaning Validation for Active Pharmaceutical Ingredients (APIs)

- This good practice applies to all GMP sites where Active Pharmaceutical Ingredients (API) are manufactured.
- Product Changeover Cleaning Procedures must be Validated for all Product Contact Equipment (both Major and Minor Equipment) used for multi-product Production, Subdivision and sampling of APIs and those Intermediate steps that are subsequent to the introduction of the API Starting Materials.
- Cleaning measures used to perform Interval Cleaning and Dedicated Equipment Campaign Cleaning shall follow Approved procedures, but are not required to be validated. Dedicated equipment Campaign cleaning shall include visual inspections for cleaning Verification.

recoveries of greater than 100 percent, no recovery values are to be used as a correction factor, but they shall have a practical upper limit.

- Training and Qualification in the use of validation sampling (swabbing and rinsate techniques), visual inspections, and analytical methods shall be part of the training Records for personnel performing these functions.

If equipment (e.g., boroscope) is used to aid in visual inspections, the user must be trained and qualified in use of the equipment.

- Validation shall consist of at least three consecutive, successful executions (i.e., no failures related to the cleaning procedure between the successful executions) of the cleaning procedure. When the Worst Case approach is used, validation trials shall be performed on the most difficult to clean compound. Also when the worst case approach is used, additional cleaning validation trials, using the next most difficult to clean product, may be conducted prior to completion of the three validation trials of the most difficult to clean product. Failure of a validation trial for the next most difficult to clean product is equivalent to a failure of the validation trial for the most difficult to clean product. Validation trials shall be executed using one or more of the following options:
 - Cleaning validation executions performed at the end of a regularly scheduled campaign; and/or
 - Changeover cleaning conducted within a campaign.
- Criteria for Equipment Cleaning Validation for major equipment shall be as follows:
 - Visibly Clean; and
 - Removal of residue (i.e., therapeutic and/or Non-Therapeutic Material) to predetermined acceptance criteria, where required. Criteria for equipment cleaning validation for minor equipment shall include the requirement to be visibly clean.
- A Validation Report referencing the relevant protocol(s) shall discuss the results from the execution of the protocol and shall be approved. A Final Report shall be issued following completion of the validation study. Interim Reports are required when the time between the start of the validation study and completion of the entire study is greater than a specified period of time.
- Any Deviation from the approved protocol shall be documented with justification. All process deviations shall also be documented and reviewed as to their impact on validation. Reports shall contain results, deviations (if any), references to cleaning procedures and protocols used, recommendations and conclusions.
- The conclusion of the report shall confirm whether the cleaning process met all of the acceptance criteria. The conclusion shall state whether the process is validated.

- Periodic Review of Validated Changeover Cleaning Procedures relative to all Equipment Units is required. The periodic review shall include the review of change control documents, cleaning procedure deviations, and cleaning result investigations. An assessment of the validated state of the cleaning procedure for the equipment shall be written into the conclusion of the Cleaning Periodic Review Report. This report must be approved by Site Quality Team and Production Team.

4. Equipment Cleaning Validation for Drug Products

- This good practice document defines the cleaning Validation requirements for GMP facilities and equipment involving the manufacturing of Drug Products.
- This procedure applies to all Pharmaceutical Production Sites where drug products are manufactured and/or packaged for Pharmaceutical or Animal Health.
- Equipment Changeover Cleaning Procedures must be validated for all Product Contact Equipment (both Major and Minor Equipment) used for multi-product production, Subdivision, and sampling of drug products and In-Process Materials.
- Cleaning Measures Used to Perform Interval Cleaning and Dedicated Equipment Campaign Cleaning shall follow Approved procedures. Interval cleaning does not require validation. Cleaning shall include visual inspections for cleaning Verification.
- Dedicated equipment cleaning validation is required for any of the following conditions:
 - When a cleaning agent is used;
 - The product is sensitive to microbiological growth; or
- To establish the product Campaign length with respect to potential microbiological contamination, using one cleaning exercise only.
- An Equipment Cleaning Validation Program shall be defined in [e.g., Validation Master Plan (VMP) or Validation Project Plan (VPP)].
- Equipment Cleaning Validation for Changeover Cleaning shall be performed by applying one of the following approaches:
 - Product Matrix (Grouping) Approach - perform validation using the most difficult to clean product(s) produced in an Equipment Train in which all the products use the same cleaning procedure (i.e., Worst Case product); or
 - Individual Product Approach - perform validation of the cleaning procedure for each product produced in an equipment train.
- Residue Acceptability Limit (RAL) for Therapeutic Dose (RAL_T) must be calculated based on each product that is to be processed in a specific equipment train. The limit for

- Validation consists of three consecutive, successful executions (i.e., no failures related to the cleaning procedure between the successful executions) of the cleaning procedure. When the product matrix (grouping) approach is used, a validation exercise shall be performed on the most difficult to clean product(s) (Marker). When the product matrix approach is used, additional cleaning validation exercises using the next most difficult to clean product may be conducted prior to completion of the three validation exercises of the most difficult to clean product (e.g., when the worst case material is made infrequently).
- Failure of a validation exercise for the next most difficult to clean product is equivalent to a failure of the validation exercise for the most difficult to clean product. Validation exercises shall be executed using one or more of the following options:
 - Cleaning validation exercises performed at the end of a regularly scheduled campaign; and/or
 - Cleaning validation exercises conducted at campaign lengths less than the maximum campaign length, as long as at least one exercise is at full campaign length.
- Criteria for Equipment Cleaning Validation for both major and minor equipment shall be as follows:
 - Visibly Clean; and
 - Analytical verification of residue removal (i.e., therapeutic and/or Non-Therapeutic Material) to predetermined acceptance criteria.
- For minor equipment, visual inspection alone is acceptable when the visual detectable quantity is at or below RAL, and there is approved documentation with justification. Safety Factor (SF) for Calculating Each Maximum Allowable Residue (MAR) for Therapeutics (MAR_T) and Non-Therapeutics (MAR_N) shall be as follows:

Safety Factor (SF) for calculating each Maximum Allowable Residue (MAR) for therapeutics (MAR_T) and Non – therapeutics (MAR_N) shall be as follows:

<u>Material</u>	<u>Safety Factor</u>
Topical products	1 / 100
Oral products	1 / 100 or 1 / 1000 ^a
Injectable products	1 / 1000
Ophthalmic products	1 / 1000
Non - therapeutics	1 / 100

Footnote (a) – A safety factor of 1 / 100 shall be used for calculation of MAR_T for oral products unless the product toxicity, potency, or safety (e.e. cytotoxic or hormones) is a concern in which case, as SF of 1 / 1000 shall be used.

procedures. The VC must approve the impact analysis of the change(s) and the determination if Revalidation or further actions are required. Such changes include, and are not limited to, those potentially affecting any of the following:

- Production process;
 - Cleaning methods;
 - Cleaning materials;
 - Sampling methods;
 - Analytical methods;
 - Microbiological methods, if applicable;
 - Equipment configuration or equipment assembly;
 - Number of Lots/Batches in a campaign;
 - Maximum time interval between use and cleaning, or between cleaning and use, if applicable;
 - Change in lot size (especially smaller);
 - Change in group of products produced in the equipment;
 - Change in equipment surface area (including piping, minor equipment, columns); and
 - Change in RAL and/or MAR.
- Periodic Review of Validated Changeover Cleaning Procedures relative to all Equipment Units is required.

5. Laboratory Equipment Qualification

- This good practice procedure defines the minimum requirements for Qualification of Simple, Moderate and Complex laboratory equipment that is used in an analytical laboratory in a Good Manufacturing Practices (GMP) environment associated with products in or intended for the marketplace.
- The extent of the qualification activities shall be defined in the Site Validation Master Plan (VMP). Laboratory equipment qualification program(s) shall be established and maintained at each GMP site (e.g., Pharmaceutical and Animal Health) defining the responsibilities, criteria and documentation requirements for the qualification of laboratory Equipment used at that Site.
- Client/server applications and Custom Software controlling laboratory equipment shall follow this procedure. The addition of new non-software laboratory equipment to existing Validated client/server or Custom Systems will follow this procedure.
- Equipment that is exempt from qualification must be defined in the Site's local Standard Operating Procedures (SOP) or VMP.
- This procedure applies to Laboratory Equipment that is used for GMP testing performed for Active Pharmaceutical Ingredients (API), API Starting Materials and Intermediates from the point at which the API starting material is introduced into the process, Drug

of training credentials shall cover tasks performed during qualification training (e.g., certificates of qualification training) and must be obtained for vendors and contractors. If training credentials are not available, the training shall be documented.

- Documentation [e.g., User Requirement Specifications (URS), Technical Manuals, Owners Manual] must be available for equipment, within the scope of this procedure, that describes what the equipment must be capable of doing in order to fulfil the needs of the laboratory.
- Qualification Testing shall verify that all components of the system meet approved pre-determined acceptance criteria. Qualification testing shall be documented.
- Installation Qualification (IQ) shall verify that all components have been properly installed and meet the manufacturer's recommendations. IQ shall be performed for simple, moderate and complex equipment. Legacy Systems do not require IQ. IQ for legacy systems shall be considered in cases of relocation or requalification.
- Operational Qualification (OQ) shall be designed to verify the equipment's operation according to pre-determined Specifications. Legacy systems OQ may be supported by an established calibration program. OQ for legacy systems shall be considered in cases of relocation or requalification.
- Performance Qualification (PQ) shall provide documented evidence that the equipment produces the intended results under normal operating conditions. Simple equipment does not require PQ. Legacy systems PQ may be supported by an established calibration program. PQ for legacy systems shall be considered in cases of relocation or requalification.
- The Completion of the Qualification Activities (i.e., IQ/OQ/PQ) shall be documented and approved by the system owner and the Quality Team signifying that the equipment is acceptable for use. Deviations resulting from execution of the qualification shall be addressed as defined in Site procedures.
- Site Defined Procedures shall be followed for any changes to the equipment after completion of qualification testing.
- Documentation for Qualified Equipment Maintenance and Operation shall be available prior to use of the equipment.
- Laboratory Equipment Requiring Ongoing Calibration shall be entered into the Site calibration program following the completion and approval of qualification activities.
- A Plan or Documented Procedure (e.g., SOP) shall be available to define the process for retiring a piece of equipment. This process shall describe all activities needed to decommission the qualified equipment including records retention.

- Microbiological Methods Validation or Verification shall be performed and documented according to an Approved Protocol that defines the parameters being evaluated, the acceptance criteria for each parameter, and the TMs. The protocol must be approved by the Lab Manager prior to execution of the validation studies.
- A Method Validation or Verification Report shall be prepared that documents the results of the validation or verification study, including the evaluation of each parameter and comparison against acceptance criteria. Any Deviations from the protocol must be documented and the impact of the deviations discussed in the report.
- Qualified Personnel shall be identified with the following roles and responsibilities in regards to microbiological test method validation or verification:
 - The Lab Manager at the Site conducting the validation or verification is responsible for assuring that the microbiological methods are validated or verified according to this procedure and for reviewing and approving the Final Report; and
 - The Quality Team, independent of the Lab Manager, at the Site conducting the validation or verification study is responsible for reviewing and approving the final report for compliance with applicable Site policies and procedures.
- Automated Systems used as a part of a microbiological test method and computer-related laboratory systems shall include Validation of the Computerized System.
- Microbiological Methods for Production Materials or Products that have Anti-microbial Activity or Inhibitory Effects on the Recovery of Microorganisms shall include a validated neutralization step, if required by the test method (e.g., Test for Specified Organisms, Microbial Limits Test).
- Qualified Personnel shall perform:
 - Validation studies, and
 - Verification of compendial methods.
- Written and Approved Procedures shall describe the preparation, labeling, storage, and use of laboratory Reagents, solutions, buffers, Reference Standards, Microbiological Culture Media, Microbial Cultures, and Biological Indicators (BI).
- Test Equipment used in the execution of the microbiological test method protocol must be Qualified and have a current Calibration status.
- Microbiological Methods Validation or Verification Studies shall be documented and retained in accordance with site record retention requirements.
- Alternative Microbiological Methods must be validated and must be shown to be equivalent to the compendial or regulatory filing method. Validated alternative microbiological methods shall be submitted to the Regulatory Team, when required, prior to implementation.

- Microorganisms used in microbiological methods validation or verification shall be specified and based on the requirements stated in the applicable compendial test chapters.
- If required by the Method, Aseptic Technique and Sterile equipment, materials and reagents shall be used during microbiological methods validation or verification.
- Due to the Inherent Variability of Some Microbiological Test Methods, the validation or verification of a microbiological method must include consideration of the following:
 - Inherent antimicrobial and/or inhibitory properties, and
 - Recovery of microorganisms from the sample.
- Pure Microbial Cultures used during microbiological methods validation or verification shall be prepared from microbiological control cultures developed by Site or purchased from a recognized culture Supplier such as American Type Culture Collection (ATCC) or National Collection Type Culture (NCTC).
- The Preparation, Growth, and Storage of Microbial Cultures shall be standardized and include, at least, the following:
 - Use of liquid cultures or confluent growths on solid media;
 - Incubation of the microbial cultures within the recommended temperature range and time; and
 - Storage of the purchased working and stock microbial cultures according to the manufacturer's recommendation.
- If Growth is Inhibited during the Test Method Verification, the method shall be modified to ensure the validity of the test results by neutralizing or removing the antimicrobial activity of the test product or material. Antibiotics may not be susceptible to neutralization by chemical means, but rather by enzymatic treatment (e.g., penicillinase). Such enzymes may be used where required.
- When Verifying a Quantitative Microbial Limits Test, the inoculation of the microbial suspension shall be added directly to the test sample preparation (product or material). When verifying a qualitative microbial limits test, the inoculation of the microbial suspension shall be added to the prescribed growth medium at the time of mixing with the test sample preparation. The inoculum size of the microbial suspension must be not more than one hundred (100) cfu and the volume of the suspension shall not exceed one percent of the volume of diluted product.
- A minimum of three (3) experiments using different product Lots, if possible, shall be conducted. The most concentrated formulation of a product shall be used for the method verification studies, as long as all other excipients are equivalent in concentration or make-up. If excipients are not equivalent in concentration or make-up, method verification studies shall be performed for all product strengths. Exceptions are permitted if the excipients in question are considered microbially inert and would have no effect upon microbial recovery.

dilution, or filtration step. (Note: This step is applicable only to quantitative tests).

3. If acceptable microbial recovery still cannot be met for one or more of the challenge microorganisms, the test method with the best microbial recovery is used to test the product or material.
- Accuracy of a non-compendial test method shall be established across a specified range of the test method:
 - Use pure microbial cultures for each microorganism that must be identified;
 - Prepare a suspension of microorganisms at the upper test range and serially dilute to the lower test range;
 - Calculate the expected cell count of the microbial culture at a minimum of five (5) serial dilutions;
 - Analyze a minimum of two (2) replicates at each of five (5) concentrations across the range of the test method; and
 - Obtain an acceptance criteria in the range of seventy (70) percent to one hundred thirty (130) percent recovery of each microorganism based on a comparison of the actual test results with the results expected from the dilutions using the upper test range used as a reference of one hundred (100) percent.
 - Precision of a non-compendial test method shall be determined as a measure of a test method's repeatability and/or reproducibility under normal operating conditions:
 - Use pure microbial cultures for each microorganism that must be identified;
 - Prepare a suspension of microorganisms at the upper test range and serially dilute to the lower test range;
 - Analyze a minimum of two (2) replicates at each of five (5) concentrations across the range of the test method;
 - Repeat the analysis on a 2nd suspension; and
 - Perform a statistical evaluation of the data [e.g. coefficient of variation (i.e., relative standard deviation) in the range of fifteen (15) percent to thirty (30) percent for an acceptable microbial count].
 - Specificity of a non-compendial test method shall be determined during validation by screening the test method against a range of representative microorganisms and sample types to demonstrate that the test method is fit for its purpose. All representative microorganisms must be successfully isolated and counted from the specified sample types.
 - Detection Limit (DL) of a non-compendial test method shall be determined by an analysis of samples with known concentrations of microorganisms:
 - Use an original sample prior to any incubation step;
 - A minimum of five (5) spiked replicates shall be evaluated for each microorganism to be detected; and
 - Establish the minimum level at which a microorganism, when present in the sample, can be detected during the time frame of the assay.

Table 1: Validation Requirements for Non-Compendial Microbiological Test Methods

Validation Parameter	Qualitative Test (Presence or Absence)	Quantitative Test
Accuracy	N/A	X
Precision - Repeatability - Reproducibility	N/A	X
Specificity	X	X
Detection Limit (DL)	X	X
Quantitation Limit (QL)	N/A	X
Linearity	N/A	X
Range	N/A	X

7. Packaging Validation

- Packaging Processes for Pharmaceutical and Animal Health products shall be Validated. This good practice guidance document addresses the validation of the primary packaging of oral solid tablets and capsules and the secondary packaging and Labeling for all Drug Products and Medical Devices.

Primary packaging of all other drug products (e.g., Sterile drug products, inhalers, solutions and suspensions and semi-solid drug products) is not addressed in this document.

- The validation approach for all commercial products and processes including packaging shall be defined in Validation Master Plans (VMP) and/or Validation Project Plans (VPP).
- This procedure applies to all pharmaceuticals Production Sites and operations responsible for packaging of commercial drug products and medical devices for Pharmaceutical and Animal Health.
- Packaging Process Validation is required in the following cases, unless there is documented justification for not performing validation:
 - Introduction of a New Product;

- Approved Specifications for finished packaged product.

Any exception to these requirements must have a documented assessment describing the impact on the validation study and the exception must be approved by the VC.

- Packaging Validation Studies must be executed using Packaging Materials with the same specifications as those intended for routine production in accordance with the following guidelines:
 - Packaging materials are purchased from an Approved Supplier;
 - A documented evaluation must be completed with regard to the impact of tablet or capsule thickness, weight, friability and breakage on the validation of the packaging process. For secondary packaging of tubes, bottles, or other containers of semisolids or liquids, an evaluation of potential leakage, breakage, and damage to the filled units must be considered;
 - A documented evaluation must be completed with regard to the impact of color on any visual sensors or staining of the equipment, where applicable;
 - The use of placebo requires precautions to be taken at the Site to assure segregation and control relative to both the placebo and use of defaced or test labeling; and
 - If final label copy is not yet approved, equivalent-labeling materials may be used with VC approval.
- Where a Change, Outside the Normal Operating Range (NOR), is Required to a Critical Process Parameter During a Validation Study the effect of the change shall be assessed for its impact on the validation study; this may include a requirement to restart the study using the new value of the parameter. The previous validation runs shall be evaluated and their Disposition documented in the report. The impact of the change on the validation shall be documented in the validation report.

Changes in non-critical process parameters may prove necessary during packaging validation to improve the performance of the packaging process while ensuring that the process produces product that meets acceptance criteria. Such changes shall be documented and justified in the validation report and evaluated for their impact on the validation exercise. Documentation and approval of such changes shall be carried out according to the relevant Site SOPs.

- Validation Test Conditions -packaging validation shall be conducted at or within the NOR defined in the packaging instructions.
- Packaging Validation Acceptance Criteria shall be established with consideration for the special needs of each product and/or process being validated. Each run shall meet acceptance criteria identified in the validation protocol. Exceptions to this must be evaluated, reviewed, and approved (if acceptable) in the validation report.
- Successful Packaging Validation Runs shall be conducted according to the packaging instructions referenced in the validation protocol.

effective. Approval of the supplemental documentation must precede execution of the change. Documentation of changes made during the validation exercise must be included or referenced in the validation report and shall include the reason for the change.

- Validation Failures - failure of any validation run to meet the requirements of the protocol shall be investigated according to site SOPs. Conclusions of the investigation shall include a determination of the effect of the run failure on the packaging validation and further actions to be taken, if any, including possible replacement of the failed validation run. Reference to the failed run and investigation shall be made in the validation report.
- A Validation Report referencing the relevant protocol(s) shall discuss the results from the execution of the protocol and shall be approved. A Final Validation Report shall be issued following completion of the validation study. Interim Validation Reports are required when the time between the start of the validation study and completion of the entire study is greater than a period of time specified in the documented Site policy.
- Any Deviation from the approved protocol shall be documented with justification. All packaging process deviations shall also be documented and reviewed as to their impact on validation.
- The conclusion of the report shall confirm whether the validation runs have met all of the acceptance criteria. The conclusion shall state whether the packaging process is validated and is approved for use in routine packaging.
- Release of Validation Lots - the conditions under which commercial lots are packaged shall comply with all regulatory registrations and other regulatory requirements. Status of validation material shall be controlled. Before a packaging validation lot can be released for commercial use or distribution, the VC shall ensure that:
 - For prospective validation, the final report is approved; and
 - For concurrent validation, at least an interim report is approved.
- Pending approval of the validation report, validation lots may be shipped to another site or Contract Vendor under Quarantine provided systems are in place to prevent commercialization of the products using this packaging process.
- Reprocessing shall be documented and evaluated as a planned deviation. The investigation shall determine the impact on the process and product. The need for and extent of requalification, Revalidation, and stability testing shall be determined by the VC and approved by the Site Quality Team and the Site Validation Team.
- Change Control - all changes that may affect product quality or reproducibility of the packaging process shall be evaluated for likely impact on the process or product. The determination of major or minor change, need for, and extent of requalification, revalidation and stability testing shall be determined by the VC.

- Process Validation shall include, at a minimum, all critical steps of the API process from the step at which the API Starting Material is introduced through all subsequent steps to the finished API. The evaluation of critical steps shall be documented and Approved by the VC.
- A step containing a parameter critical to the quality of the final API is deemed a critical process step and shall be included in the validation.
- A Validation Protocol shall be established that specifies how validation will be conducted. The protocol shall specify critical steps, Critical Process Parameters, sampling requirements and acceptance criteria, and shall be approved before validation activities begin.
- The extent of the validation effort shall be based on a Risk Assessment.
- Prospective Validation shall be used in validating a substantially modified or new process.
- Retrospective Validation of legacy processes may be used in a few specific circumstances. The decision to carry out retrospective validation shall be documented and justified. The decision to use retrospective validation shall be approved by the VC.
- Concurrent Validation may be used for well-understood and documented processes. The decision to carry out concurrent validation shall be documented and justified. The decision to use concurrent validation shall be approved by the VC.
- Prerequisites for Process Validation include, and are not limited to, the following:
 - Approved Master Manufacturing Process Instructions, Manufacturing Process Instructions, Records and applicable Standard Operating Procedures (SOP);
 - Identified critical process parameters and Critical Quality Attributes;
 - Qualified equipment, facilities, utilities and Computerized Systems. Exceptions to this requirement must be approved by the VC;
 - Qualified or validated supporting processes that may affect process validation (e.g., Filtration or Sterilization);
 - Compatibility with product-contact equipment for leachables and extractables;
 - Calibration of critical instruments;
 - Approved Specifications for finished product and Raw Materials (RM) and established In-Process Controls (IPC) and decision criteria for them;
 - Validated Test Methods required for release of products . Suitably qualified or validated test methods shall be used to support non-routine data generated during validation studies; and
 - Qualified personnel to prepare the validation Batches and perform other work associated with the validation study.
- Any exception to these requirements must have a documented assessment describing the impact on the validation study and the exception must be approved by the VC.

established limits or be within justified statistical limits (e.g., +/-3 sigma around the mean) of historical data. Alternative equivalence criteria must be justified and approved. Equivalence of other critical chemical and physical attributes shall also be demonstrated.

- Validation Test Conditions -process validation shall be conducted using standard production conditions. Evaluation of challenge conditions that pose the greatest chance of process or product failure compared to ideal operating conditions shall be documented during process development and/or process robustness studies.
- Processing Time Limits -if a specific processing time (e.g., normal or extended processing time of an in-process solution or suspension) is critical to product quality, evaluation of the limits for the processing time shall be conducted in a manner such as that used for critical process parameters.
For biopharmaceutical processes:
 - The biochemical stability of process intermediates under processing conditions (e.g., due to pauses in processing) shall be demonstrated either at manufacturing scale or lab scale. This can be accomplished at manufacturing scale by conducting studies using samples of process intermediates taken from the full scale DS manufacturing process (e.g., by holding of samples rather than holding the full-scale batch);
 - Processing time limits shall be designed to account only for the stability of individual pools. Cumulative processing time studies representing the summation of maximum unit operation processing times are not required. Hold time for materials used in the process (such as for buffers or growth media) shall be established when there is potential impact on product quality.
- Bracketing or Matrixing may be used where multiple Process Parameters or equivalent Equipment Items are involved. The purpose and rationale for the bracketing or matrixing approach used must be documented and justified in the validation protocol.
- Validation Batch Size shall be the same size as the intended standard commercial scale batches. Normal allowed variations in linear scale changes shall be specified in Site SOPs with justification. Where ranges in batch size outside of the normal allowed variation are proposed for the commercial process, it must be demonstrated or justified that variations in batch size do not adversely alter the characteristics of the finished product.
- For synthetic processes, small-scale commercial batches may be validated where the manufacture of full-scale intended commercial size batches is not practical.
- A concurrent validation approach may be used for linear scale changes from the validated batch size. The Number of Process Validation Batches prepared and data collected shall be sufficient to provide enough data for the evaluation of process reproducibility.
- For new processes or validation of major process changes, a minimum of three consecutive batches is typical for process validation. Use of a different number of validation batches (i.e. other than 3) must be documented and justified, based on process

- The work shall be discontinued and restarted following approval of a new, revised protocol that includes the reason for the change; or
 - Supplemental documentation shall be prepared, approved, and issued via the same approval process as followed for the original protocol. The supplement shall specify the reason for the change and the point in the protocol at which it becomes effective. Approval of the supplemental documentation must precede execution of the change. Documentation of changes made during the validation exercise must be included or referenced in the validation report and shall include the reason for the change.
- Data Verification -relevant batch documentation shall be reviewed according to Site SOPs prior to inclusion in the validation protocol or report. The data in a validation protocol or report shall also be independently verified, as indicated by signature and date of the verifier, to confirm that information such as test results have been accurately transferred from the original documents or recorded data.
 - Validation Failures -failure of any validation batch to meet the requirements of the protocol shall be investigated according to Site SOPs. Conclusions of the investigation shall include a determination of the effect of the batch failure on the process validation and further actions to be taken, if any, including possible replacement of the failed validation batch. Reference to the failing batch and investigation shall be made in the validation report.
 - A Validation Report referencing the relevant protocol(s) shall discuss the results from the execution of the protocol and shall be approved. A Final Report shall be issued following completion of the validation study. Interim Reports are required when the time between the start of the validation study and completion of the entire study is greater than a specified period of time, per documented Site policy.
 - Any Deviation from the approved protocol shall be documented with justification. All process deviations shall also be documented and reviewed as to their impact on validation.
 - The conclusion of the report shall confirm whether the validation batches have met all of the acceptance criteria. The conclusion shall state whether the process is validated and is approved for use in routine manufacturing.
 - Release of Validation Batches -the conditions under which commercial batches are produced shall comply with all regulatory registrations and other regulatory requirements. Status of validation material shall be controlled.
 - Before a validation batch can be released for commercial use or distribution, the VC shall ensure that:
 - For prospective validation, the final report is approved; and
 - For concurrent validation, at least an interim report is approved.

- Minor changes may require a documented, expanded test program or other evaluation using the Site change management system.
- Periodic Review is required as described in site policy. Such periodic reviews shall consist of a documentation review of manufacturing and analytical Records, including deviations, investigations, process Trends and change control documents and shall verify that:
 - The systems and processes are still operating in a validated state of control; and
 - There have not been major changes to the process either as single changes or as cumulative changes.
- If the review findings indicate the process is not under control, an investigation shall be conducted to determine impact on the process and product, and to determine potential need for revalidation, and/or any other corrective actions.
- Record Retention -process validation records shall be held at the manufacturing location according to the site requirements.

9. Process Validation for Drug Products and Medical Devices

- This guidance document applies to all GMP production site and operations responsible for manufacturing commercial drug products, biopharmaceuticals, medical devices and in-process materials used in the production of commercial drug products.
- Production Processes used for producing a Drug Product, Medical Devices, biopharmaceuticals or In-Process Material for a drug product shall be Validated.
- All commercial products and processes at the GMP site and the validation approach for each process shall be defined in Validation Master Plans (VMP) and/or Validation Project Plans (VPP).
- Process validation shall include critical steps in the manufacturing and filling of the product into the primary package for those dosage forms where the filling process may potentially affect a Critical Quality Attribute. Filling of tablets and capsules and Labeling and secondary packaging of all drug products and medical devices are defined in point 7 of this document.
- Process validation for medical devices shall include the processes to manufacture Component(s) of the device and the assembly processes employed to build a finished medical device.
- This procedure addresses process validation and Revalidation of existing, new and modified processes used for production of commercial drug products and medical devices

- Qualified personnel to manufacture the validation Batches or Lots and perform other work associated with the validation study.
- Any exception to these requirements must have a documented assessment describing the impact on the validation study and such exceptions must be approved by the VC.
- Raw Materials (RM) and Components used in the manufacture of validation batches/lots shall be purchased, stored and approved according to site procedure.
- Critical Process Parameters, Critical Process Parameter Ranges, and Critical Quality Attributes of the process being validated must be identified and justified.
- The VC is responsible for ensuring that the ranges proposed in the validation protocol for critical process parameters are correct and have supporting documentation. Such information shall be obtained from, for example, the technical transfer information, design of experiments (DOE), or historical Site documentation, and shall be included or referenced in the validation protocol.
- Where a Change is Required to a Critical Process Parameter During the Validation Study, the effect of the change shall be assessed for its impact on the validation study. For medical devices, this assessment shall include evaluation of the impact of the change on device functionality (safety and efficacy), and the capability of assembly process.
- The change may require restarting the validation study using the new critical process parameter value(s). The previous validation batches/lots shall be evaluated and their Disposition documented in the report. The assessment of the impact of the change on the validation study shall be documented in the validation report.
- Changes in non-critical process parameters may prove necessary during process validation to improve the performance of the process while ensuring that the process produces product that meets acceptance criteria. Such changes shall be documented and justified in the validation report and evaluated for their impact (individual and cumulative) on the validation exercise.
- Documentation and approval of such changes shall be carried out according to the relevant Site SOP.
- Validation Test Conditions -process validation shall be conducted using standard production conditions as defined in the approved Master Manufacturing Process Instructions or approved DMR for medical devices, and the applicable SOPs referenced in the validation protocol.
- Evaluation of challenge conditions that pose the greatest chance of process or product failure compared to ideal operating conditions shall be documented during process development and/or process robustness studies.

- Homogeneity (Including Blend Uniformity) shall be included or referenced in the validation protocol for drug product and medical device process steps where homogeneity is defined as a critical attribute.
- Homogeneity shall be demonstrated for a modified process, when assessment of a planned change indicates a potential impact on batch homogeneity.
- Biopharmaceutical Processes typically involve steps where evidence of adequate mixing must be demonstrated during full-scale validation. If homogeneity or Mixing Studies are not performed as part of process validation, a documented rationale explaining why this study was not necessary shall be provided or referenced in validation documentation.
- Stability Requirements -samples from at least one batch/lot manufactured according to the validated process and meeting the stability testing requirements defined in site policy shall be placed on stability if one of following situations occurs:
 - For processes that are new to a site,
 - For a reformulated product, or
 - Where it is believed that the change may affect stability (e.g., a Rework process, lengthening of the bulk hold time, new medical device component).
- Changes to Approved Protocols -where a change to an approved protocol is required prior to the start of execution, the protocol shall be reissued as the next version and shall be approved by the same approval authorities as the original protocol before starting the validation exercise.
- When a change that impacts an acceptance criterion is needed after protocol execution has already begun, options that must be considered are:
 - The work shall be discontinued and restarted following approval of a new, revised protocol that includes the rationale for the change; or
 - Supplemental documentation shall be prepared, approved, and issued via the same approval process as followed for the original protocol. The supplement shall specify the rationale for the change and the point in the protocol at which it becomes Effective. Approval of the supplemental documentation must precede execution of the change.
- Documentation of changes made during the validation exercise must be included or referenced in the validation report and shall include the rationale for the change.
- Data Verification -relevant batch/lot documentation shall be reviewed according to Site SOPs prior to inclusion in the validation protocol or report. The data in a validation protocol or report shall also be independently verified, as indicated by signature and date of the verifier, to confirm that information such as test results, data summaries and graphs have been accurately transferred from the original documents or recorded data.
- Validation Failures -failure of any validation batch/lot to meet the requirements of the protocol shall be investigated according to Site SOPs. Conclusions of the investigation

- Reprocessing that is applied to the majority of batches shall be included as part of the standard manufacturing process and shall be included in the validation of that process."
- Change Control -all changes that may affect product quality or reproducibility of the process shall be evaluated for likely impact on the process or product. The VC shall determine whether the change is a major or minor change, and the impact on the validation status and/or stability testing.
- If validation of a process involves a regulatory change, a Product Change Proposal (PCP) and a Product Change Request (PCR) are required.
- Major changes to raw materials, components, equipment, utilities, facility, procedures, or process require validation.
- Minor changes may require a documented, expanded test program or other evaluation using the Site change management system.
- To Change an Active Pharmaceutical Ingredients (API) Supplier, validation work must be conducted following an approved protocol that demonstrates the change will have no adverse impact on finished drug products, medical devices or processes.
- Periodic Review is required as described in site procedure. A documentation review of manufacturing and analytical records, including deviations, investigations, process Trends (if there are sufficient data) and change control documents shall verify that:
 - The processes are operating in a validated state of control; and
 - There have not been major changes to the process either as single changes or as cumulative changes.
- If the review findings indicate the process is not in a state of control, an investigation shall be conducted to determine the impact on the process and product, and to determine the potential need for revalidation and/or any corrective actions.
- Record Retention -all process validation records shall be held at the manufacturing location according to the requirements stated in site policy.

10. System Validation

- This practice defines the validation requirements for Systems (facilities, utilities and equipment, including process control systems, process analytical technology systems and information systems) that support Regulatory Compliance and used in the production or storage and distribution of Active Pharmaceutical Ingredients (API), Intermediates, Drug Products, Medical Devices or Biologics.

- Change Management Procedure(s) shall be established and internal and External Consultants conducting validation activities shall be trained to perform their specific tasks. Training shall be documented in the form of work instruction or manual.
- Standard Operating Procedures (SOP) shall be prepared, approved and implemented.
- The Quality Authority at each GMP site shall approve the validation documents and shall be responsible for ensuring the implementation of established validation Systems.
- Information Technology (IT) subject matter experts such as site IT shall serve as the Quality Authority and approve all validation and related documentation for IT infrastructure for which they are responsible to manage.

11. Validating Aseptic Processing - Active Pharmaceutical Ingredients (API)

- This guidance document defines the Validation requirements for aseptic processing of an Active Pharmaceutical Ingredient (API) in a defined manufacturing system configuration using aseptic processing simulation tests.
- This procedure applies to all GMP sites where APIs are aseptically processed.
- Aseptic Processing Simulation Tests shall be performed according to an Approved Protocol and shall simulate the process from the point of Sterilization through to the completion of the manufacturing and packaging operations, including any aseptic operation(s) performed during API compounding. The aseptic processing simulation test shall include any material holding times in the processing equipment after the material is considered Sterile.
- Aseptic Processing Simulation Tests shall not increase the potential for microbial, particulate, or other contamination of the manufacturing system or the API.
- Aseptic Processing Simulation Test Materials shall be received and processed in the same manner as Raw Materials. Testing and release requirements shall be defined by Specifications.
- Processes and Support Systems Directly Affecting Production of Sterile APIs shall be qualified and/or validated prior to conducting aseptic processing simulation tests and shall include, and not be limited to, the following:
 - Water treatment and distribution systems;
 - Compressed gas and process gas systems;
 - Filtration Systems (i.e., liquid, gas, and vent);
 - Clean Steam generation and distribution systems;
 - Heat exchange systems;
 - Vacuum systems;

taken and the required new aseptic processing simulation tests are successfully completed.

- An Aseptic Processing Simulation Test shall be invalidated when events unrelated to aseptic processing occur that impact the validity of the simulation. An aseptic processing simulation test shall be declared invalid when any of the following conditions occur:
 - Failure of the Growth Promotion Test; or
 - Incorrect incubation conditions (e.g., exceeding the maximum incubation temperature limit).
- In the case of a Microbiological Culture Medium growth promotion test failure, an aseptic processing simulation test shall be declared invalid. The manufacturing system can be used for production on a temporary basis, if the cause for the microbiological 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.
- When there is no assignable cause for the microbiological culture medium growth promotion failure, the manufacturing system shall not be used for production until remedial action has been taken and a new aseptic processing simulation test is successfully completed.
- Aseptic Processing Simulation Tests applicable to the process include, and are not limited to:
 - Equipment sterilization,
 - Aseptic addition of materials to previously sterilized vessels,
 - Transitions between vessels,
 - Milling,
 - Vessels under vacuum (pneumatic transfer equipment),
 - Aseptic manipulations,
 - Sampling, and
 - Final primary packaging of the API.
- Aseptic Processing Simulation Tests shall include, and not be limited to, the following:
 - For initial validation of aseptic processing, a minimum of 3 consecutive, successful simulations (i.e., no failures with no process related assignable cause between the successful executions) performed on separate days and/or shifts;
 - For routine Revalidation of aseptic processing, one successful process simulation test performed at least every two years;
 - All personnel who perform aseptic processing or aseptic processing support activities to be included in at least one aseptic processing simulation test every two years;
 - Be of sufficient duration to simulate all typical activities and interventions; and
 - Simulate aseptic processing from the point of sterilization to the final API packaging step.

- Aseptic Processing Simulation Testing shall be performed as either:
 - A single continuous test that simulates the entire aseptic processing configuration; or
 - A series of individual unit operations, including transitions between discrete unit operations and holding times that are part of the operation, which when combined simulate the entire aseptic processing configuration (e.g., liquid phase and dry phase).

- Test Results From Each Unit Operation in an Aseptic Processing Simulation shall be cumulative when calculating the microbial contamination of the entire process. If any unit operation fails, the entire aseptic processing simulation fails. Aseptic processing simulation need only be repeated for the failing unit operation.

- Aseptic Processing Simulations requiring blanketing with sterile, inert gas shall use sterile air in order not to inhibit growth when aerobic incubation conditions are employed.

- Aseptic Processing Simulation Tests shall be performed prior to the next scheduled requalification in the case of the following events:
 - Confirmed sterility test failure where an investigation concludes the need for requalification; and/or
 - When there has been a significant change. Examples of such changes include, but are not limited to:
 - (a) Changes to the manufacturing process and/or associated systems;
 - (b) Modifications to equipment directly contacting the API or API-contact surfaces of Containers;
 - (c) Changes to the quality of airflow that directly contacts API contact surfaces;
 - (d) Major changes of production personnel (e.g., addition of one or more new shift, new group of operating personnel); and
 - (e) Procedural changes potentially affecting aseptic processing.

- Powdered Simulation Test Material shall be reconstituted with either:
 - A sterile diluent, such as WFI, when it is subsequently membrane filtered prior to testing for microbial contamination; or
 - Sterile liquid microbiological culture medium, when the simulation test material is incubated directly.

- Incubation Chambers shall be qualified, Calibrated, alarmed and continuously monitored throughout the incubation period.

- Test Samples shall be incubated for a minimum of 7 calendar days at 20 -25o C followed by a minimum of 7 calendar days at 30 -35o C.

- Growth Promotion Testing, in which the simulation test material is tested for potential inhibition, shall be performed using microorganisms selected according to the applicable Compendia and at least one isolate taken from the environment for which optimum

- An Event Log shall be maintained by a qualified person in the Aseptic Processing Area (APA) during each aseptic processing simulation test to record events (e.g., unplanned interventions) and observations that are not addressed in the aseptic processing simulation test protocol. The event logs shall be reviewed by the validation committee and the review documented. The event logs shall be retained according to site validation documentation retention policies.
- Aseptic processing simulation tests may also be videotaped. If the Aseptic processing simulation is videotaped, the videotape must be reviewed by a qualified person and the results summarized and included in the final report. Videotapes shall be retained according to site validation documentation retention policies
- Microorganisms found in contaminated units shall be subjected to genus and species identification methodology.
- An Investigation shall be conducted for an aseptic processing simulation test failure and shall include, and is not limited to, consideration of the following:
 - Environmental and personnel monitoring data;
 - All sterilization process data including calibration data;
 - APA cleaning and sanitization;
 - APA and APA Support Personnel training;
 - HEPA Filter Integrity;
 - Sterilizing Filter Integrity;
 - Equipment cleaning, sterilization and operation;
 - Manufacturing process; and
 - Identification of the microbial contaminant(s).
- When an Aseptic Processing Simulation Test Fails Due to an Assignable Cause, corrective action must be taken and documented. The root cause and the corrective action shall dictate the number of aseptic processing simulation tests required to demonstrate that the process is operating within the expected parameters. When an assignable cause is identified for a failing test, the rationale for product disposition shall be documented.
- When an Aseptic Processing Simulation Test Fails and There is No Assignable Cause, the aseptic processing must be revalidated with a minimum of three consecutive, successful aseptic processing simulation tests completed prior to using the aseptic process for sterile API manufacturing.
- In Case of a Failure Where There is No Assignable Cause, the investigation shall include a review of all batches/lots produced since the last successful aseptic processing simulation test.
- Change Control and Revalidation Measures shall be implemented for all aseptic processing operations to identify, document, and review changes (e.g., to equipment, procedures, cleaning, and sterilization) that impact the validated state of the aseptic processing operation. The Validation Committee (VC) shall:

- Selection of Analytical Methods for use in Equipment Cleaning shall include consideration of the following factors:
 - Type of residue being measured (e.g., organic, inorganic);
 - Sampling method (e.g., swab or Rinsate); and
 - Residue Acceptability Limits (RAL) in the analytical sample.

- Use of a Specific or a Non-Specific Method is acceptable for determining residues after cleaning. If a specific method is used, it must be capable of detecting and quantifying the analyte of interest in the presence of other materials that may also be present in the sample. If a non-specific method [e.g., Total Organic Carbon (TOC)] is used the response must be considered to be from the analyte of interest.

- Analytical Methods, Including the Sampling Methods used to determine residues after cleaning must be validated.

- Validation of Analytical Methods Used to Detect Residue in Equipment shall include consideration of the following characteristics:
 - Specificity,
 - Linearity,
 - Sensitivity,
 - Repeatability and Recovery,
 - Stability of the standard and sample (swab and rinse solutions); and
 - Intermediate Precision.

- Sensitivity of Analytical Methods must be sufficient to detect [Detection Limit (DL)] and quantify [Quantitation Limit (QL)] the target analyte at or below its established RAL.

- The Swab Sampling Technique must address the following factors:
 - Swab type (including wipes) and size;
 - Composition of the swabbing solvent (i.e., solution that is used to wet the swab prior to sampling of the equipment surface); and
 - Composition of the swab recovery solution (i.e., solution used for extraction).
Swabbing Techniques must be described or referenced in a Standard Operating Procedure (SOP).

- The Stability of Residue on Swabs (i.e., stability performed on stored swabs) shall be determined.

- Analyte Residue Recovery, which includes recovery of the analyte from both a representative equipment surface and the sampling technique (e.g., swab), shall be challenged as part of the analytical method validation. These challenges must demonstrate that analyte residues are recoverable from expected product contact surface material and the sampling material per the requirements of this procedure.

- A Method Validation Protocol must be prepared to document the validation parameters being evaluated, the acceptance criteria for each parameter and the Test Methods (TM). The protocol must be Approved by the Lab Manager prior to execution of

- Compliance with written Site requirements and quality standards; and
 - Authorization to implement.
- Site Quality Team SMEs must review and approve the following validation documentation types, where applicable:
 - Plans,
 - Science and risk based assessments,
 - Tests and/or acceptance criteria for critical aspects,
 - Final Design Review, and
 - Reports.
 - Other principals [e.g., System Owner, Production, Technical Services, Engineering, Information Technology (IT), other SMEs] may review and approve validation documents, as needed and may be part of a committee [e.g., Validation Committee (VC)].
 - Current Elements of the Validation Program shall be defined and documented [e.g., in a Validation Master Plan (VMP), Site Standard Operating Procedures (SOPs)]. Such documentation shall contain information on at least the following:
 - Validation approach or policy;
 - Summary of facilities, equipment, systems and processes to be validated;
 - Organizational structure of validation activities;
 - Planning and scheduling (e.g., what needs to be done when);
 - Change management;
 - Reference to existing documentation (e.g., individual discipline validation plans for cleaning and production processes, project verification plans, SOPs).
 - A Validation Plan [e.g., Validation Project Plan (VPP), Project Commissioning and Qualification Plan (PCQP), Verification Plan (VP), change control document, testing document, Protocol, SOP] shall be used to document validation activities.
 - The Scope of Validation, at a minimum, shall include those areas of potential risk to product quality, patient safety and/ or regulatory compliance. If a risk based approach is used to narrow the scope of validation, the approach shall be documented [e.g., Impact Assessment, quality Risk Assessment, functional assessment, Failure Mode & Effects Analysis (FMEA)].
 - Prospective Validation is the preferred validation approach. The use of Concurrent Validation, or Retrospective Validation approaches and associated rationale for using the approach of choice shall be documented (e.g. in a VMP, VP, PCQP, or protocol) and approved.
 - System Documentation [e.g., User Requirement Specifications (URS), Requirements Document, Specifications, Vendor Operation and Maintenance Manuals, Purchase Order, Product and Process Development Reports, Formulation Development Summary] must be available that describes the system including what the system does, and how the

- Facilities, Systems, Equipment and Processes, Including Cleaning, shall be periodically evaluated (e.g., Periodic Review) to confirm that they remain validated. The frequency of periodic evaluation shall be based on risk.
- This evaluation shall be documented and approved. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for Revalidation.