

1. PURPOSE

This policy establishes guidance and minimum requirements to assure that Waters' processes, methods, facilities or equipment produce a result or product that meets predetermined criteria for critical to quality attributes. These guidelines are designed to ensure compliance with appropriate FDA regulations and International Quality System requirements, including but not restricted to 21CFR Part 820, ISO-9001, and ISO-13485.

2. SCOPE

The policy applies to Waters' sites where validation is a regulatory requirement.

This policy addresses validation/qualification of:

- Manufacturing processes
- Test Methods
- Facilities
- Equipment

This policy excludes the following:

- This policy does not apply to design validation
- This policy does not apply to the manufacture of product not intended for commercial distribution (e.g. prototype, engineering batches, trial batches, etc)
- This policy excludes software validation and the validation of software tools as defined in Policy 730000617

3. DEFINITIONS AND ABBREVIATIONS

Term	Definition / Abbreviation
Concurrent Validation	Validation with the intention of distributing product manufactured during the process validation and is based on data generated during routine production.
CTQ	Critical to Quality Attributes: Attributes which have shown through Risk Management, requirement, and/or specifications that they may have direct or indirect effect on the quality of the product.
Deviation	Failure to follow the prescribed protocol sequence, materials, equipment, methods, or acceptance criteria. This could be proactive or after the fact.
Equipment	An organization of engineering components that have a defined operational function
Equipment Qualification (EQ)	Establishing by objective evidence that equipment consistently operates according to intended use.

GDP	Good Documentation Practices, as defined in Waters' Good Documentation Procedure 730000523
Installation Qualification (IQ)	Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to approved specifications and that the recommendations of the supplier of the equipment are suitably considered.
Test Method	A defined analytical process that produces a test result
Operational Qualification (OQ)	Establishing by objective evidence process control limits and action levels which result in product that meets all predetermined acceptance criteria.
Performance Qualification (PQ)	Establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined acceptance criteria.
Process	An activity or group of activities that takes an input, adds value to it, and provides an output to an internal or external consumer; a planned and repetitive sequence of steps by which a defined product or service is delivered.
Process Validation	Establishing by objective evidence that a process consistently produces a result or product meeting its predetermined acceptance criteria.
Prospective Validation	Validation which is conducted prior to the distribution of either a new product, or product made under a revised process where the revisions may have affected the product's specifications and quality attributes.
Test Method Validation	Confirmation by objective evidence that the test method is appropriate.
Retrospective Validation	Establishing through documented evidence that an existing process or equipment consistently produces a product which meets all predetermined acceptance criteria. It is generally used for product already in distribution and utilizes a review and critical analysis of historical process and product data
Qualification	A series of inspections and tests to ensure that critical requirements necessary for product quality are satisfied, and that documents and procedures necessary to properly operate and maintain the system are in place.
Validation	Confirmation by examination and objective evidence that the particular requirements for a specific intended use <u>can be consistently</u> fulfilled.
Verification	Confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled.
Fully Verify	Confirmation that specified requirements have been fulfilled through 100% inspection with a non-destructive test.
VMP	A summary of the overall strategy for conducting validation activities at a facility. The Validation Master Plan describes the validation overview, approach, and status of each manufacturing process, test method and/or equipment.

4. ROLES AND RESPONSIBILITIES

Roles	Responsibilities
Waters Corporate Management	It is the responsibility of Waters Corporate Management to allocate sufficient resources necessary for the implementation of this policy.
Waters Site Management	It is the responsibility of Waters Site Management to ensure implementation of this policy at each site.
Waters Site Quality Groups	The Quality group is responsible for ensuring this policy is complied with when performing, documenting and/or reviewing site specific Validation/Qualification activities.

5. REFERENCES / RELATED DOCUMENTS

Doc No:	Document Title
730000617	CSV: Global Software Tool Val Policy
730000523	Good Documentation Practices (GDP)
730000295MP	Quality System Document Control
WAT000050MP	Waters Record Retention Corporate Policy
N/A	GHTF “Quality Management Systems - Process Validation Guidance”, 2004
N/A	21 CFR Part 820 - Quality System Regulation, Version: Current version referenced within Waters Business Operations Quality Manual
N/A	ISO 9001, Version: Current version referenced within Waters Business Operations Quality Manual
N/A	ISO-13485, Version: Current version referenced within Waters Business Operations Quality Manual

6. GUIDANCE AND REQUIREMENTS

6.1. General

6.1.1. This policy provides the overall framework for developing site specific procedures and templates. Decisions as to what level (extent and complexity) to validate items should be based on a documented and justified rationale. Risk assessment tools shall be used for the development of a scalable validation strategy that enables selection of appropriate activities for a specific equipment/method /process. Any decision should be justified and documented within the validation documentation.

6.1.2. There are three (3) interlinking categories of validation; Equipment Qualification, Test Method Validation and Process Validation. The validation categories should be performed in the following sequence:

6.1.2.1. Equipment Qualification (EQ)

6.1.2.1.1. All equipment within a method or process should undergo qualification prior to validation of the method or process

6.1.2.1.2. Equipment used in production of product within a fully verified process must undergo equipment qualification

6.1.2.2. Test Method Validation (MV)

6.1.2.2.1. All test methods within a process should be validated prior to the validation of that process

6.1.2.2.2. All test methods shall be validated if the method is used in the verification of a process

6.1.2.3. Process Validation (PV)

6.1.2.3.1. A process should be validated only after all major equipment has been qualified and the test methods have also been validated within that process

6.2. Equipment Qualification

6.2.1. The purpose of EQ is to ensure equipment is installed correctly and operates to manufacturer's guidelines or Waters requirements through predetermined acceptance criteria.

6.2.2. Equipment that is used in the manufacturing process or monitoring of product must undergo qualification (including, but not limited to, calibration, and/or validation). This work flow is illustrated in Figure 1.

6.2.2.1. This decision flow was designed to encompass a majority of use cases and should be used as a guide. The decision flow may vary depending on the size and complexity of the equipment.

6.2.2.2. Calibration is considered a form of qualification but the calibration process is not required to adhere to the guidelines of this policy.

6.2.3. Software that is considered part of the equipment (e.g. test equipment software) can be qualified as part of equipment qualification.

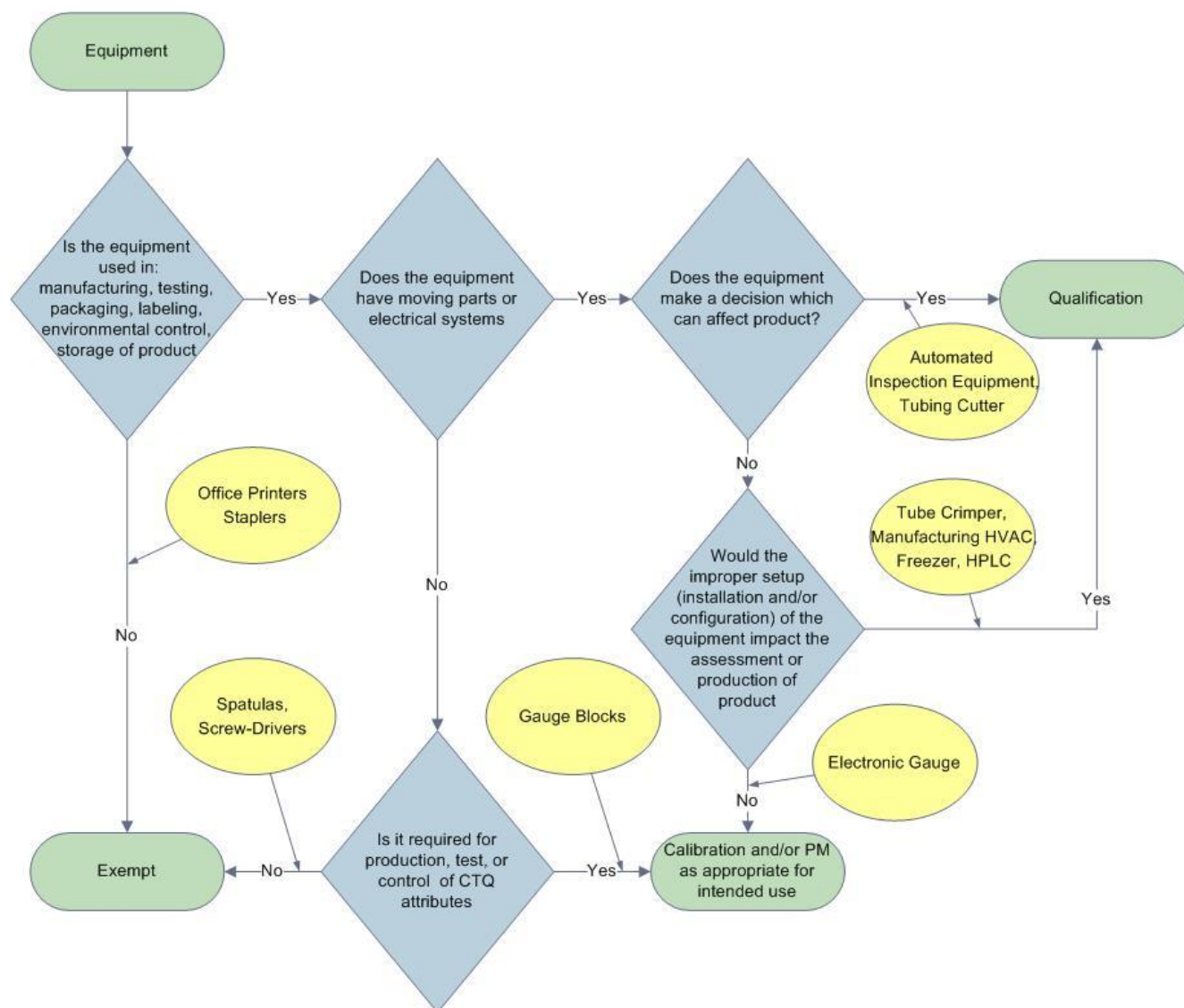


Figure 1: Equipment Qualification Decision Flow

6.3. Test Method Validation

6.3.1. Test methods that are used for the release of product, in-process testing, or in the evaluation of qualification/validation outputs shall be validated where the test methods are employed.

6.3.2. All equipment used within the test method should be qualified prior to test method validation.

6.3.3. At a minimum, validation of a test method shall evaluate the accuracy and precision of the method. Additional attributes may be evaluated at the discretion of the site where the test method is being employed. These attributes may include (but are not limited to) the following.

6.3.3.1. Reproducibility

6.3.3.2. Repeatability

6.3.3.3. Linearity and Range

6.3.3.4. Limit of Detection

6.3.3.5. Specificity

6.3.4. Pre-determined acceptance criteria for each attribute should be stated in the validation protocol as well as in the validation summary report.

6.4. Process Validation

6.4.1. Manufacturing processes shall be validated at the site where the process is being performed.

6.4.2. Process Validation vs. Verification

6.4.2.1. Validation is required if the process CTQ attributes are **not** fully verified.

6.4.2.2. It is important to consider if full verification is cost effective.

6.4.2.3. It may become apparent that the process may not be validated because the key variables cannot be adequately controlled to mitigate risks or assure consistent results in the product. Redesign of the product or process may be required if key variables cannot be adequately controlled. The process must be reassessed, using the decision tree, if the product or process is modified.

6.4.2.4. Test methods must be validated and equipment qualified which are used during verification testing.

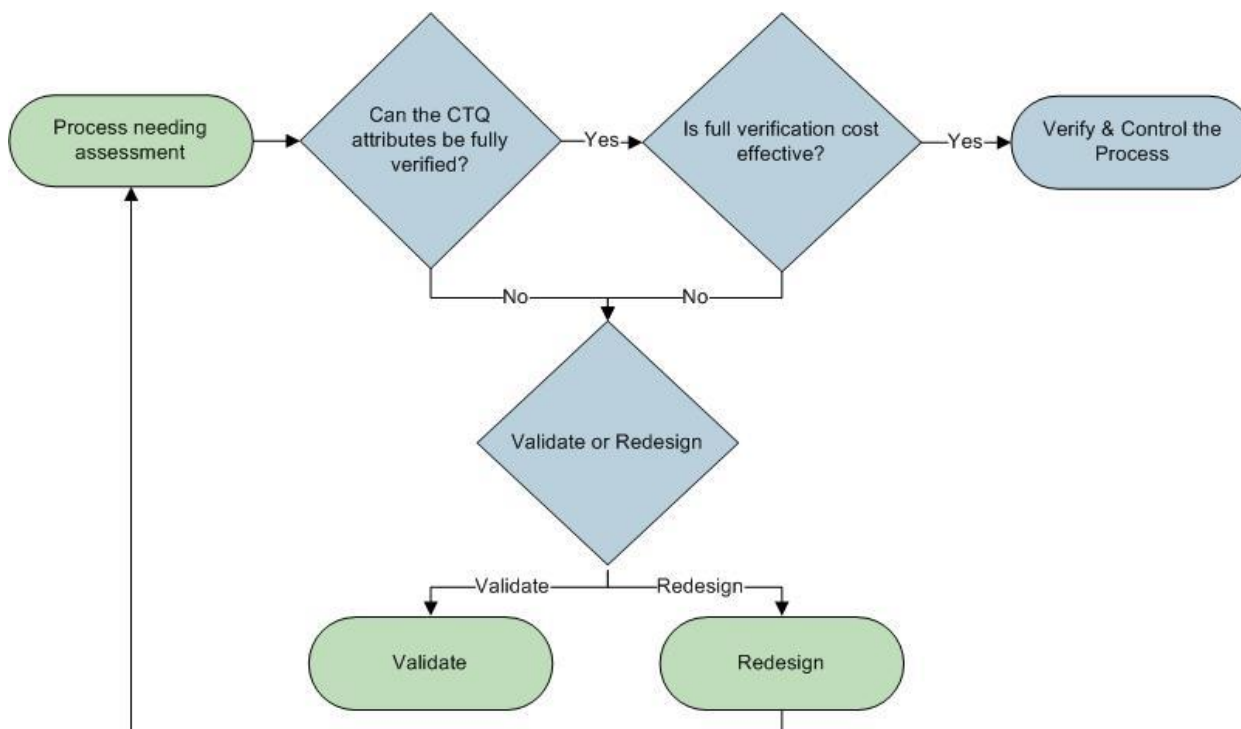


Figure 2. Validation versus verification decision tree

6.4.3. Protocols of Process Validation: The three essential protocols to process validation are listed below. Protocols for process validation should be separated by approval but may be combined or excluded with justification.

6.4.3.1. Installation qualification (IQ) ensures all key aspects of the equipment and ancillary system are installed correctly. All of the required EQ should be performed as a sub-element of the IQ.

6.4.3.2. Operational qualification (OQ): ensures that the process are meeting the control limits throughout the intended operating range.

6.4.3.3. Performance qualification (PQ): ensures that the processes, under normal operating conditions consistently produces product which meets predetermined requirements.

6.4.4. At the foundation of process validation is a Validation Plan (6.5.2) which organizes the elements of validation: the qualifications of equipment within the process, the validations of the Test Methods within the process, and the validation protocols (IQ, OQ, PQ). This concept is illustrated in Figure 3.

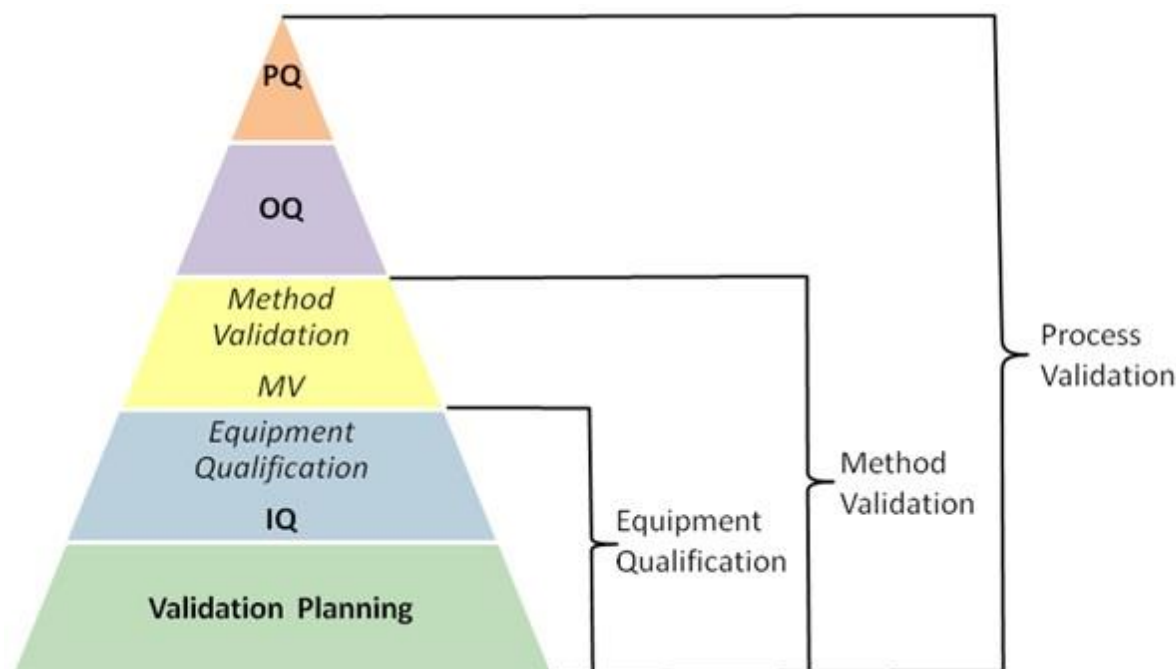


Figure 3: Elements of Process Validation

6.5. Validation Planning

6.5.1. Validation Master Plan

6.5.1.1. Each site shall create and maintain a Validation Master Plan (VMP). Due to the various businesses within the corporation and the differing applicable regulations, each site shall define the additional specific requirements for the individual site Validation Master Plans within their local procedures.

- 6.5.1.2.** Validation to be performed shall be based upon site-specific risk assessment activities related to site-specific equipment, test methods and/or manufacturing processes. These activities shall be documented using site-specific Validation Master Plans (VMP).
- 6.5.1.3.** The evaluation of processes and their subsequent prioritization in the Validation Master Plan (if applicable) shall be determined through a risk based approach. The minimum requirements for the Validation Master Plan are as follows:
 - 6.5.1.3.1.** The VMP is to be reviewed on an annual basis or more frequently based on need
 - 6.5.1.3.2.** Identification of the equipment, methods and/or processes to be validated/qualified
 - 6.5.1.3.3.** Validation Status
 - 6.5.1.3.4.** Responsibility allocated where applicable
 - 6.5.1.3.5.** Target completion date or time frame where applicable

6.5.2. Validation Plan

- 6.5.2.1.** The validation plan may be described within the protocol or as a separate document depending on the complexity of the project.
- 6.5.2.2.** The plan must address the following:
 - 6.5.2.2.1.** Define the team and their responsibilities
 - 6.5.2.2.2.** Define and justify the type of validation (e.g. prospective, concurrent)
 - 6.5.2.2.3.** Identify and describe the equipment/method/process being validated
 - 6.5.2.2.4.** Plan the approach and justify the level of validation required, based on risk
 - 6.5.2.2.5.** Determine new or revised documentation/deliverables required, e.g. IQ, OQ, PQ, SOP's, training, risk assessments, software development documents, etc.

6.5.3. Validation Classifications

- 6.5.3.1.** Prospective validation should be performed on all new equipment/methods/processes prior to production use.
- 6.5.3.2.** Concurrent validation may be performed on legacy equipment/methods/processes that are currently used in production.
- 6.5.3.3.** Retrospective validation may be performed on legacy equipment/methods/processes with justification only if the quality of the historical data set allows for adequate analysis.

6.6. Legacy Validation

6.6.1. If a change has been implemented to a legacy process/method/equipment it shall fall under the standard validation/qualification work flow.

6.6.2. Legacy Equipment

6.6.2.1. For legacy equipment that has already been installed and operating in production, the qualification should focus on critical requirements and intended use of the equipment in the protocol.

6.6.3. Legacy Test Methods

6.6.3.1. All legacy test methods that are part of legacy processes should be evaluated for accuracy and reproducibility, and validated where required.

6.6.4. Legacy Processes

6.6.4.1. Process data of CTQ attributes should be collected, either retrospectively or concurrently for the process under evaluation. The data should be analyzed using appropriate statistical methods (e.g. control charts). Assess if the process is in a statistical state of control which falls within established specification limits.

6.6.4.2. If the process is demonstrated to be in a statistical state of control then no further action is required, process monitoring continues, and the process is considered validated. The analysis conclusion must be documented in a summary report.

6.6.4.3. If negative quality trends are observed, they are investigated to determine the root cause, and if a change to the process is needed. These changes may require process validation to be completed prior to release of the process for routine production. Concurrent validation could be used in this instance but must be justified.

6.7. Vendor Validation

6.7.1. Vendor performed validation may use the procedures and documentation provided by the vendor in place of Waters' validation procedures provided they have been pre-approved locally by Engineering and Quality Assurance.

6.7.2. Care should be taken to ensure that acceptance criteria within vendor provided documentation meets Waters' intended use.

6.8. Revalidation

6.8.1. Revalidation or requalification may be performed on the process/method/equipment under certain conditions. Examples include but are not restricted to:

6.8.1.1. Change(s) in process/method/equipment have occurred that could affect product quality

6.8.1.2. Transfer/moving of the process/method/equipment

6.8.1.3. Observed negative trends (e.g. CAPAs or NCRs) related to a process/method/equipment

6.8.1.4. Change(s) in product design which affects the process/method/equipment

6.8.1.5. Periodic requalification (clean-rooms)

6.8.2. Revalidation may not be as extensive as the initial validation (partial validation) if the situation does not require that all aspects of the original validation be repeated. The

justification shall be based on the type of change, the complexity of the process/equipment, and the risk involved.

6.9. Documentation Requirements

6.9.1. The minimum requirements for a correctly executed validation shall consist of an approved protocol, validation plan (which may be included with the protocol) and a summary report (which also may be included within the protocol).

6.9.2. The validation/qualification process demonstrates that a process/method/equipment meets intended use by producing an expected result. The validation protocol and report will include the following elements, where applicable:

- 6.9.2.1.** Identification and complete description of the equipment/method/process to be validated
- 6.9.2.2.** Objective and measurable acceptance criteria for successful validation
- 6.9.2.3.** Identification of utilities for the process equipment and quality of utilities
- 6.9.2.4.** Required training
- 6.9.2.5.** Relevant specifications that relate to the equipment/method/process
- 6.9.2.6.** Any special controls or conditions to be placed on preceding processes during the validation
- 6.9.2.7.** Parameters to be monitored and methods for controlling and monitoring
- 6.9.2.8.** Product characteristics to be monitored and method for monitoring
- 6.9.2.9.** Disposition of product used or produced during the execution of the validation.
- 6.9.2.10.** Validation documentation shall be approved prior to execution (i.e. protocol, plans) and after execution (i.e. summary report).
- 6.9.2.11.** Appropriate statistical methods for data collection and analysis
- 6.9.2.12.** Deviations (see 6.9.3)
- 6.9.2.13.** Results and outcomes

6.9.3. Deviations

- 6.9.3.1.** Any discrepancy from the approved protocol (including but not restricted to nonconformances to acceptance criteria or variance from protocol parameters) is considered a deviation.
- 6.9.3.2.** Typographical or administrative errors are exempt from deviations. These typographical errors may be addressed within the protocol following Waters' GDP outlined in [730000523](#). All errors which affect the original intent of the protocol, such as errors within the acceptance criteria, do not qualify as typographical or administrative errors.
- 6.9.3.3.** Each deviation should be addressed, investigated, and resolved prior to the completion of the validation.
- 6.9.3.4.** The validation protocol/report shall address any deviations that may have occurred during the execution of a given validation protocol.
- 6.9.3.5.** Accepted deviations shall include a documented rationale based on risk as the impact of the integrity of the validation.

6.9.3.6. If the deviation affects the integrity of the validation:

6.9.3.6.1. Modifications to the validation protocol or equipment/method/process may be necessary

6.9.3.6.2. The validation should be partially or fully re-executed unless justification is provided

6.9.4. Validation/Qualification Summary

6.9.4.1. After validation/qualification protocols have been executed, a report or summary statement should be written to summarize the results, conclusions, and if applicable, deviation resolutions of the validation/qualification activities

6.10. Personnel

6.10.1. A team approach to validation/qualification should be given strong consideration as there are few systems that function in isolation. Validation/qualification activities should be undertaken by a cross functional team including, but not limited to, process owner/system owner, subject matter expert, and quality representation.

6.10.2. All personnel involved in a validation/qualification must be suitably trained for the functions they will perform. This training must be documented.

6.11. Documentation

6.11.1. All validation documentation must undergo quality review and approval.

6.11.2. Validation documentation must be maintained per the requirements of Quality System Document Control, [730000295MP](#) and retained in accordance to Waters Record Retention Corporate Policy, [WAT000050MP](#).

6.11.3. All documentation must follow Waters' Good Documentation Practices described in [730000523](#).

DOCUMENT HISTORY

VERSION:	03	ORIGINATOR:	Michelle Farley	Change ID:	N/A
SUMMARY OF CHANGE: Version 03 changes consist of formatting corrections and an update of the Validation Master Plan definition.					
VERSION:	02	ORIGINATOR:	Michelle Farley	Change ID:	N/A
SUMMARY OF CHANGE: This version, 02, is a complete rewrite of the current policy for simplification of the validation process moving forward.					
VERSION:	01	ORIGINATOR:	Claire Spalding	Change ID:	N/A
SUMMARY OF CHANGE: Version 01 was abandoned					
VERSION:	00	ORIGINATOR:	Wendy Baker	Change ID:	N/A
SUMMARY OF CHANGE: Version 00 is the first document					