

Process Validation Procedure

Document # 730001835

Version # 08

Page 1 of 17

1. Δ PURPOSE

The purpose of this procedure is to define and manage the validation process and deliverables for manufacturing processes, test methods, and equipment.

2. Δ SCOPE

The scope of this procedure are Waters LC manufacturing Processes, test methods, and equipment; purchased, designed and/or constructed, which reside in Milford MA production; LC equipment which reside in Singapore Operations Contract Manufacturing sites; and Waters owned LC Product support assets that reside at distribution centers.

All validation activities performed prior to the release of this procedure remain valid.

Validation deliverables performed and/or provided by outside parties may cover the intent of applicable validation requirements, provided the defined requirements are met, which would preclude the requirement of using the defined documents of this procedure.

This procedure excludes the following:

- Design Validation
- The manufacture of product not intended for commercial distribution
- Software Validation and the validation of software tools as defined in 730000617, CSV: Global Software Tool Val Policy.

3. Δ DEFINITIONS AND ABBREVIATIONS

Term	Definition / Explanation
Analytical Test Method	A Test Method used to setup and/or run a system that evaluates product CTQs.
Attribute Data	Test inspection whereby either the UUT is classified as conforming or nonconforming with respect to a given requirement.
Calibration	A process to ensure that equipment is capable of producing accurate results. This includes verifying measurements and/or making adjustment(s) to ensure measurement accuracy.
Confidence	The probability that a value will fall within defined specifications.
Critical to Quality (CTQ) 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.
Custom Test Software	Specially written software used to automate and/or make pass/fail decisions for conformance of Waters products specifications.
DIR	Document Information Records
Equipment	An organization of engineering components that have a defined operational function.
Equipment Design Verification (EDV)	A document and activity that verifies the design functionality of the equipment in accordance with the operational requirements.
Equipment Qualification (EQ)	Establishing by objective evidence that equipment consistently operates according to intended use.
External Measurement	A measurement taken from non-Waters, third party equipment, such as gauges, meters, scales, etc.

Process Validation Procedure

Document # 730001835

Version # 08

Page 2 of 17

Term	Definition / Explanation
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.
In Vitro Diagnostics (IVD)	Any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information.
Internal Measurement	A measurement taken from Waters product.
LC	Liquid Chromatography
Legacy Equipment	Production equipment, test methods, or processes (non-IVD) that have already been installed and operating in production prior to 2016 and are excluded from the VMP as they have been proven over time to verify and/or produce acceptable product.
N/A	Not Applicable
Operational Qualification (OQ)	Establishing by objective evidence process control limits and action levels which result in product that meets all predetermined acceptance criteria.
PC	Personal Computer
Preventive Maintenance (PM)	The servicing, for the purpose of maintaining equipment in satisfactory working order, by performing systematic inspection, detection, and correction of potential failures. PM activities may include tests, measurements and parts replacement.
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 (PV)	Establishing by objective evidence that a process consistently produces a result or product meeting its predetermined requirements.
Production Support Checks (PSC)	Tests performed in support of product design specifications to assure product quality, and/or verify pre/post test conditions.
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.
Reliability	The percentage that a manufacturing process produces product that meets specified CTQ requirements.
Risk	A combination of the probability of detection and the severity of potential harm.
SAP	Enterprise Resource Planning (ERP) software
TE	Test Equipment or Test Engineering
Test Method	A defined analytical process that produces a test result.
Test Method Validation (TMV)	Confirmation by objective evidence that the test method is appropriate, accurate and precise.

Process Validation Procedure

Document # 730001835

Version # 08

Page 3 of 17

Term	Definition / Explanation
Test Specification and Procedure (TSP)	A step-by-step detail of how to run the test system.
UUT	Unit Under Test
Validation	Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.
Validation Assessment Form (VAF)	A document that outlines the qualification approach to be taken based on a risk assessment of an engineering change to an existing manufacturing process, test method, or piece of equipment.
Validation Master Plan (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.
Validation Report (VR)	A document that summarizes the validation and/or qualification activities.
Variable Data	Measurements using a continuous scale, such as weight, length, strength, etc.
Verification	Confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled.

4. ROLES AND RESPONSIBILITIES

Roles	Responsibilities
Originator	- Write the VMP Submission Form for new equipment, test methods or processes - Write the VAF for changes to existing equipment or processes - Write/coordinate the writing of the applicable protocols - Coordinate the execution of the applicable protocols - Write/coordinate the writing of the applicable reports
Originator or Executor	- Execute the applicable approved protocols - Document any deviations or failures that occur and the resolution taken - Provide all objective evidence and/or data
VMP Coordinator	- Edit the VMP based on the submitted VMP Submission Form or VAF - File all approved hard copy documents
Reviewer (as required)	Review and/or approve the applicable documents (VAF, protocol, reports) to ensure compliance to this procedure, regulatory requirements and departmental procedures
Approver (Site Quality or Operations Delegate)	
Management	- It is the responsibility of management to ensure implementation of this procedure and affiliated Standard Operation Procedures (SOP) - Review and/or approve all necessary documentation deliverables - Assign resources as required to support validation activities

Process Validation Procedure

Document # 730001835

Version # 08

Page 4 of 17

5. RELATED DOCUMENTS

Doc #	Document Title
730000617	CSV: Global Software Tool Val Policy
730000837	Waters Global Validation Policy
730004135	Installation Qualification Protocol
730001936	Test Method Validation Protocol

6. FORMS / TEMPLATES

Doc #	Document Title
730001937	Equipment Design Verification Protocol Template
730001938	VAF Template
730004131	VMP Submission Form
730004136	Operational Qualification Protocol Template
730004137	Performance Qualification Protocol Template

6.1. Validation Records

All deliverables (qualification documents) shall be captured in SAP. The qualification documents shall be associated with the appropriate equipment or process number (TE or VAL) in SAP, as defined in the protocol and report templates, but in the cases where the equipment predates this procedure, the records may be stored in a physical folder defined by the system owner.

DIR's for documents associated with equipment designed by Test Engineering shall use "TE0" for the class code and a six (6) digit core number normally based on the five (5) digit equipment number with a zero (0) preceding (Example: TE0084000QA). A suffix of QA shall be used to store unexecuted, approved qualification documents. A suffix of QX shall be used to store executed, approved design level qualification documents, such as an EDV Report. A 2-digit numerical suffix, based on the individual station number, shall be used to store executed, approved duplicate test station qualification documents, such as an IQ Report.

Non-Test Engineering processes, test methods, and equipment document DIR's shall use "VAL" for the class code and a six (6) digit core number that will be assigned by SAP (Example: VAL001200). All Non-Test Engineering Protocols and Reports will be saved within this SAP DIR.

Process Validation Procedure

Document # 730001835

Version # 08

Page 5 of 17

The Equipment/Process documents stored in SAP are structured as follows:

DIR and Description	Stored Deliverables
TE00XXXXXQA / VAL0XXXXX Quality Document: This contains the qualification protocols.	• Equipment Design Verification Protocol (EDV) • Operational Qualification Protocol (OQ) • Performance Qualification Protocol (PQ)
TE00XXXXXQX / VAL0XXXXX Executed design-level Quality Document: This contains all documents related to the execution of a design-level test protocol, including an associated system design report.	• Validation Assessment Form (VAF) [design-level] • Equipment Design Verification Report (EDVR) • Test Method Validation Report (TMVR)
TE00XXXXX01 ... TE00XXXXX99 / VAL0XXXXX (The TE DIR 2-digit suffix is based on the duplicate test station number) Executed individual station Quality Document: This contains all non-design documents related to the qualification or validation of an individual system. This will require revision anytime a protocol is run for any individual test system or process.	• VMP Submission Form • Validation Assessment Form (VAF) [system-level] • Installation Qualification Report (IQR) • Operational Qualification Report (OQR) • Performance Qualification Report (PQR)

Note: All listed deliverables may not be required. Refer to the appropriate risk assessment and/or procedure to clarify required deliverables.

7. HEALTH & SAFETY

No Health & Safety specific considerations.

Should anyone following this instruction identify a health and safety hazard which has not been highlighted in this section and/or within the body of the text, they should notify their Manager/ Supervisor immediately.

7.1. Equipment/Materials of use Required

Not Applicable

Process Validation Procedure

Document # 730001835

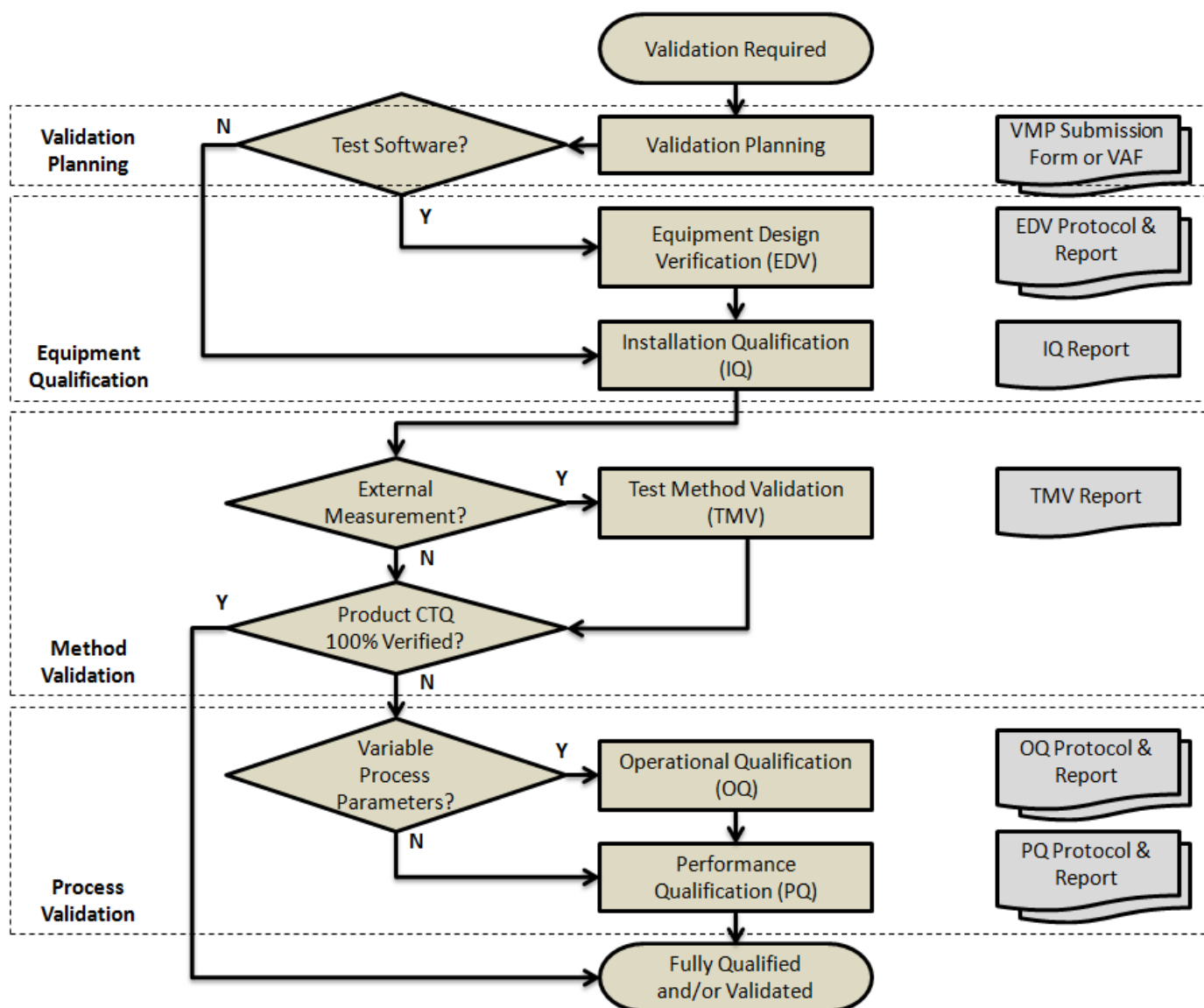
Version # 08

Page 6 of 17

8. PROCEDURE

8.1. General Overview

All equipment, test methods, and processes that requires validation, as determined by 730000837, Waters Global Validation Policy shall utilize the following high-level Decision Flow Tree to make decisions as to the qualification and/or validation activities required. For specific details of process steps and decisions refer to the Process Flow Chart in Appendix A.



8.1.1. Process Validation for Milford and Singapore Sites Decision Flow Tree

Process Validation Procedure

Document # 730001835

Version # 08

Page 7 of 17

8.2. Validation Planning

Validation Planning defines the equipment or process validation activities.

8.2.1. Validation Master Plan (VMP)

The Validation Master Plan shall be maintained by the site VMP Coordinator and shall list all applicable site manufacturing processes, test methods, and equipment that require qualification, in order to track, schedule, and prioritize the site validation activities.

- 8.2.1.1. All new manufacturing processes, test methods, and equipment that have been deemed to require process validation, whether purchased, designed, and/or constructed by Waters, shall be added to the VMP.
- 8.2.1.2. New manufacturing processes, test methods, and equipment shall require the completion of 730004131, VMP Submission Form in order to be added to the VMP.
- 8.2.1.3. Δ Validation activities shall be listed on the VMP with the appropriate status:
 - **Pending:** Validation activities that are awaiting resources and/or system availability.
 - **Active:** Validation activities that are in process.
 - **Complete:** Validation activities that have had all deliverables completed.
- 8.2.1.4. Δ Validation activities shall be assigned a priority based on the risk assessment of changes, functionality of the system, and/or production scheduling, as follows:
 - **Urgent:** Validation activities that require immediate action (Line down, non-conformance/compliance, etc.).
 - **Normal:** Validation activities that do not require immediate action (Future, production expansion, process improvement, etc.).
 - **Low Impact:** Manufacturing processes, test methods, or equipment that have a minimal effect on the product or are tested during later production steps.
- 8.2.1.5. The VMP shall be reviewed at least annually.

8.2.2. Validation Assessment Form (VAF)

Any change to manufacturing processes, test methods, or equipment that require process validation necessitates the system owner to determine the level of qualification or requalification required, based on a risk assessment.

8.2.2.1. Risk Assessment

The qualification requirements of an existing manufacturing process, test method, and equipment shall be determined by analyzing the likelihood of the change causing a faulty product and the potential customer impact.

Δ The change shall be risk assessed as Low, Medium, or High, as follows:

- **Low:** An inadequate or improperly performed change shall not cause a safety hazard and/or poor performance.
- **Medium:** An inadequate or improperly performed change has the potential to cause a safety hazard and/or poor performance.
- **High:** An inadequate or improperly performed change has a high probability of causing a safety hazard and/or poor performance.

Process Validation Procedure

Document # 730001835

Version # 08

Page 8 of 17

Examples of changes, the associated risk level, and the requalification or revalidation requirements, are provided in the table below. The following list is not fully encompassing.

Low	Medium	High
- Document changes - Replacement of identical components - Calibration/Preventive Maintenance	- Part number adds - Instrument firmware updates - PC operating system updates - Local physical moves - Replacement of non-identical components - Minor software improvements	- Significant software/ hardware changes - Specification changes - Firmware updates for a station that downloads firmware - Physical moves to different sites
Excluded from further qualification activities	- VAF required - No EDV or TMV - IQ, OQ, PQ as appropriate	- VAF required - EDV, TMV, IQ, OQ, PQ as appropriate

- 8.2.2.1. Changes to legacy equipment shall not require TMV unless the change alters an external measurement device.
- 8.2.2.2. Changes to manufacturing processes, test methods, and equipment that are of a medium or high risk shall require the completion of the 730001938, Validation Assessment Form.
- 8.2.2.3. Δ A manufacturing process or system that has previously had a full Installation Qualification performed and that results in the requirement of a partial execution, based on the risk assessment, as defined in Section 8.2.2. of this procedure, may be approved by designated Manufacturing Operations Engineering personnel.

8.3. Equipment Design Verification (EDV)

All equipment designed with custom test software shall be subjected to an Equipment Design Verification (EDV) to prove the design of the system and/or the ability to accurately make pass/fail decisions. Custom spreadsheets and other formula driven scripts, used for CTQ support calculations and/or decision-making, shall be subject to an EDV.

- 8.3.1. An EDV Protocol, specific to the custom test software/system design, shall be written using 730001937, EDV Protocol Template.
- 8.3.2. The EDV shall be executed once per production equipment design.

8.4. Installation Qualification (IQ)

All manufacturing processes and/or equipment shall be installed according to the manufacturer's recommendations and Waters' requirements.

- 8.4.1. The installation of site manufacturing processes or production equipment is performed by executing 730004135, Installation Qualification Protocol.
- 8.4.2. Δ A manufacturing process or production equipment that has previously had a full Installation Qualification performed and that results in the requirement of a partial execution, based on the risk assessment, as defined in Section 8.2.2. of this procedure, may be approved by designated Manufacturing Operations Engineering personnel.

Process Validation Procedure

Document # 730001835

Version # 08

Page 9 of 17

8.5. Test Method Validation (TMV)

Test Method Validation is required for any test method or measurement system that is using an external measurement device and/or is subject to operator induced variation.

- 8.5.1. TMV shall document the activities that verified that an external measurement device or test method is acceptable for the specification under test.
- 8.5.2. Δ TMV may be performed for analytical Test Methods, when appropriate.
- 8.5.3. TMV of site manufacturing processes and/or production equipment is performed by executing 730001936, TMV Protocol.

8.6. CTQ Attribute Verification

Any process where the Critical to Quality (CTQ) attributes will not be 100% verified requires Process Validation.

- 8.6.1. The CTQs shall be defined and/or referenced in supporting validation documents, such as Quality Inspection Plans, User Requirements Specification, the Test Specification and Procedure (TSP), and/or design prints.
- 8.6.2. For Test Engineering systems, the TSP shall include all applicable design inputs, as well as system PSCs.
- 8.6.3. The Process Validation includes an Operational Qualification and/or Performance Qualification.

8.7. Operational Qualification (OQ)

The OQ protocol shall be used to establish confidence that the system is capable of producing acceptable product throughout the intended operating range.

- 8.7.1. The OQ shall be performed only for manufacturing processes that have variable system parameters with process control limits which can affect the product meeting all predetermined acceptance criteria.
- 8.7.2. The OQ of site manufacturing processes is performed by executing an OQ Protocol, written in accordance with the 730004136, Operational Qualification Protocol Template.
- 8.7.3. The OQ sampling plan has been developed using a risk-based approach, focused on risk to the consumer, as defined in Section 8.9 of this procedure.

8.8. Performance Qualification (PQ)

The PQ protocol shall be used to establish confidence that the system, under normal operating conditions, is capable of consistently producing acceptable product.

- 8.8.1. The Performance Qualification of site manufacturing processes is performed by executing a PQ Protocol, written in accordance with the 730004137, Performance Qualification Protocol Template.
- 8.8.2. The PQ sampling plan has been developed using a risk-based approach, focused on risk to the consumer, as defined in Section 8.9 of this procedure.
- 8.8.3. Δ Once validated the site manufacturing process shall be monitored in order to ensure that it remains in a state of control. The responsibility of establishing the statistically relevant control levels, based on risk, resides with the process owner and shall be documented in an associated controlled document.

Process Validation Procedure

Document # 730001835

Version # 08

Page 10 of 17

8.9. Sampling Plans

The number of devices that needs to be tested in order to validate a manufacturing process depends on numerous factors, including, but not limited to, the level of risk, the type of data being measured, and the levels of confidence and reliability desired.

8.9.1. Risk Based Approach

The levels of AQL, LTPD, Producer Risk, and Consumer Risk, defined below, which result in the overall OQ/PQ sampling plan levels, were defined by Waters' Management, based on the overall risk the site is willing to accept as determined by the end use of our products.

8.9.1.1. Acceptable Quality Level (AQL)

The Acceptable Quality Level (AQL) is the maximum number of defective goods considered acceptable in a particular sample size.

8.9.1.1.1. An AQL level of 1% has been defined for all products.

8.9.1.2. Rejectable Quality Level (RQL)

The Rejectable Quality Level (RQL), also known as the Lot Tolerance Percent Defective (LTPD), is the poorest level of quality that the consumer is willing to tolerate in an independent lot.

8.9.1.2.1. An RQL level of 10% has been defined for all product CTQ's.

8.9.1.2.2. This RQL results in an overall Reliability Level of 90%.

8.9.1.3. Producer's Risk

The Producer's Risk, α , also known as Type I error, is the probability that a good product (a lot with less than or equal to the defined Acceptable Quality Level (AQL)) will be rejected as a bad product.

8.9.1.3.1. A Producer's Risk level of 0.05 has been set for all CTQ's of all manufacturing processes.

8.9.1.4. Consumer's Risk

The Consumer's Risk, β , also known as Type II error, is the probability, for a given sampling plan, of accepting a lot with a defect level equal to the Lot Tolerance Percent Defective (LTPD).

8.9.1.4.1. Three levels of Consumer's Risk (Low, Medium, and High), based on the severity of the function of the end product(s) being tested and the level of detectability, has been defined.

8.9.1.4.2. Detectability (Within site Manufacturing)

The levels of Detectability are based on whether the UUT component, sub-assembly, or assembly that the process that is being validated manufactures, will be tested, normally as part of a sub-assembly or assembly, during later production steps, and that failure of the CTQs are likely to be observed during that testing.

Detectable: All of the components, sub-assemblies, and/or assemblies that the process that is being validated manufactures is tested during later production steps and functionality is verified during that testing.

Partially Detectable: A portion of components, sub-assemblies, and/or assemblies that the process that is being validated manufactures is tested during later production steps and/or a portion of the functionality is verified during that testing.

Undetectable: None of the components, sub-assemblies, and/or assemblies that the process that is being validated manufactures is tested during later production steps and/or none of the functionality is verified during later testing.

Process Validation Procedure

Document # 730001835

Version # 08

Page 11 of 17

8.9.1.4.3. Severity

The levels of severity are based on the end use of the Site products and/or whether a fault of the component, sub-assemblies, and/or assemblies that the process that is being validated manufactures would cause poor performance of the final product.

Poor performance is defined as the final assembly's or sub-assembly's critical-to-quality specifications being negatively impacted and/or safety safeguards being compromised.

Minor: Component, sub-assembly, and/or assembly that the process that is being validated manufactures will not cause poor performance.

Moderate: Component, sub-assembly, and/or assembly that the process that is being validated manufactures may cause poor performance.

Major: Component, sub-assembly, and/or assembly that the process that is being validated manufactures will cause poor performance.

8.9.1.4.4. Determine the appropriate Consumer's Risk level from the table below:

Detectability	Severity		
	Minor	Moderate	Major
Detectable	Low	Low	Medium
Partially Detectable	Low	Medium	High
Undetectable	Medium	High	High

8.9.1.4.5. The levels of Consumer Risk are provided below:

Risk Levels	Low	0.15	Medium	0.10	High	0.05
-------------	-----	------	--------	------	------	------

8.9.1.4.6. The risk assessment and the resulting risk level shall be defined within the associated Operational Qualification Protocol and/or Performance Qualification Protocol.

8.9.1.4.7. The Consumer's Risk level results in an overall sampling Confidence Level which is a percentage based on the following formula:

$$\text{Confidence} = 1 - \beta$$

For example, a 0.05 Consumer Risk equates to a Confidence Level of 95%.

8.9.2. Data Type

The sampling plan or plans required for validating a manufacturing process shall be based on the type of data that is being measured. The sample size for OQ and PQ testing, which will be calculated using the Producer's Risk and Consumer's Risk as defined above, based on the defined AQL and RQL, will vary, depending on whether the data is attribute or variable.

8.9.2.1. Attribute Data Sampling

Attribute Data is data that have a quality characteristic (attribute) that meets, or does not meet, product specification and is usually collected when standard measurements are difficult, or not possible to obtain. Attribute Data is often evaluated as either pass or fail or is compared with visual standards. Due to the limited information obtained through attribute data the number of required samples, as compared to variable data sampling, is normally higher.

8.9.2.1.1. The attribute data sampling requirements result in a plan that defines both the number of samples required and number of defects permitted.

Process Validation Procedure

Document # 730001835

Version # 08

Page 12 of 17

8.9.2.2. Variable Data Sampling

Variable Data is data that has a changing (measurable) value. Variable Data is normally compared to an acceptable specification limit (either lower or upper) or a range that is defined by both a lower and an upper specification.

8.9.2.2.1. The variable data sampling requirements result in a plan that defines both the number of samples required and the associated lowest k value (Tolerance Interval), which will be used as part of the Acceptance Criteria.

8.9.2.3. Once the Consumer Risk, and whether Attribute Data or Variable Data has been defined, the Originator of the OQ and/or PQ Protocol shall use the Risk-Based Statistical Criteria for Process Validation Table, provided below, to define the required number of samples. The number of permitted defects, for attribute data, and the associated k value, for variable data, is provided.

Risk-Based Statistical Criteria for Process Validation					
Validation Element	Confidence (1 – β)	Attribute Data Sampling Plan		Variable Data Sampling Plan	
		Samples	Defects Permitted	Samples	Lowest k Value
OQ / PQ	95%	61	2	27	1.80395
	90%	52	2	20	1.73910
	85%	33	1	16	1.68541

8.9.2.4. Samples used for Process Validation are permitted to be used as production parts provided the testing was non-destructive, does not affect the sample's functional integrity, and the units met the specified acceptance criteria.

8.9.2.4.1. Samples shall be quarantined by the area Supervisor until the associated Qualification and/or Validation Report(s) is/are approved.

8.9.2.5. The above provided sampling plans were determined using Minitab® Statistical Software. It is recommended to use Minitab® to calculate the acceptance criteria calculations, as defined in Appendix B. Manual acceptance criteria calculations may be performed and are provided as reference in Appendix B, Section 2, Calculating Acceptance Criteria Values.

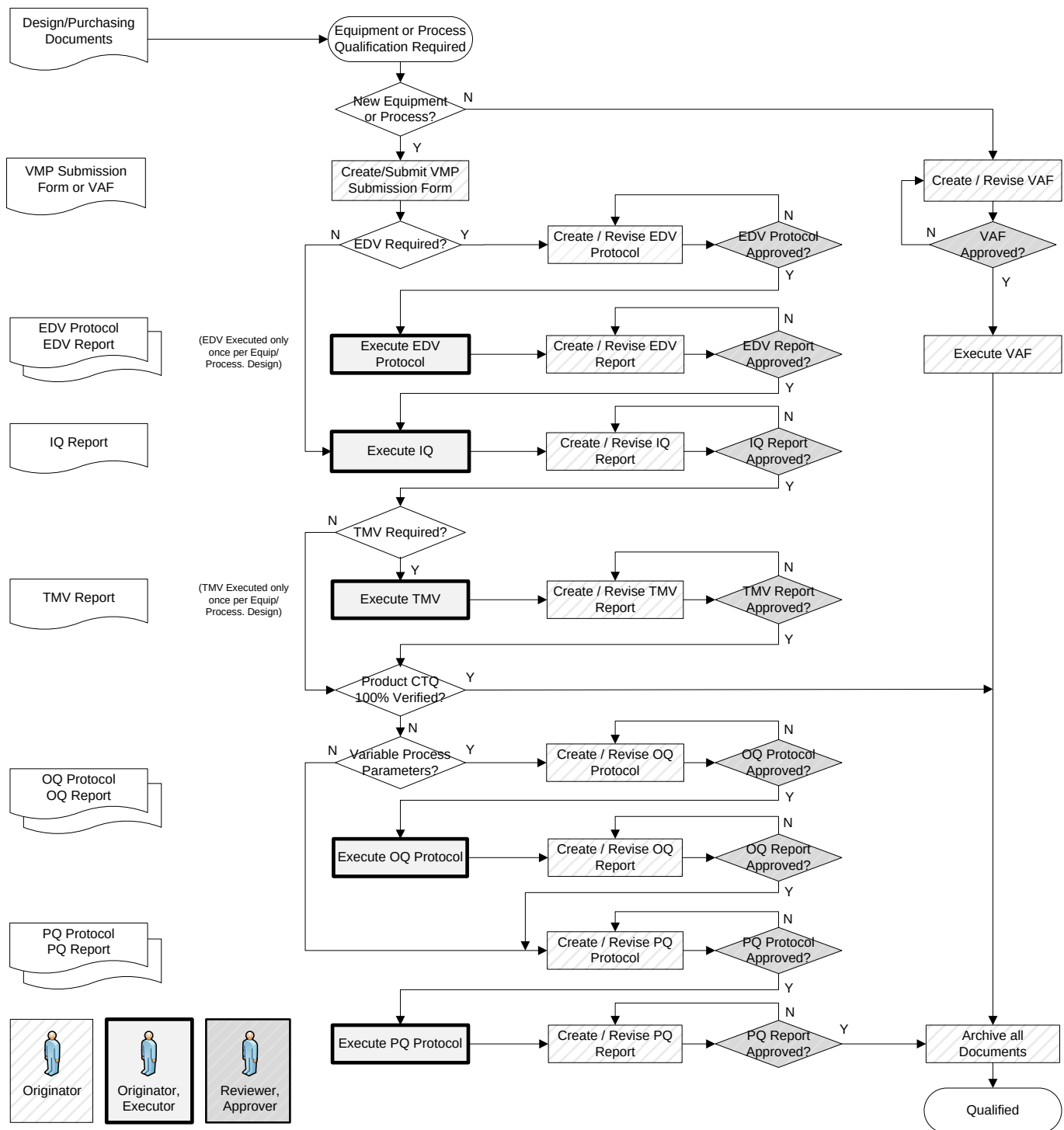
Process Validation Procedure

Document # 730001835

Version # 08

Page 13 of 17

APPENDIX A: PROCESS FLOW CHART



Process Validation Procedure

Document # 730001835

Version # 08

Page 14 of 17

APPENDIX B

1. OQ/PQ SAMPLING PLAN ACCEPTANCE CRITERIA

1.1. The Acceptance Criteria varies depending on the sampling plan selected and whether the data is attribute or variable, and if variable, whether it is for one-sided or two-sided tolerance specifications.

1.1.1. Attribute Sampling Plan Acceptance Criteria

Attribute sampling plans shall meet the defects permitted, where all devices tested must meet the test specifications, with the exception of a number of the devices tested equal to or less than the defects permitted, in order for a site manufacturing process to be considered validated.

1.1.2. Variable Sampling Plan Acceptance Criteria

One-sided tolerance limit variable sampling plans use the following acceptance criteria for a site manufacturing process to be considered validated:

1.1.2.1. For one-sided tolerance limit – lower specification: $Z.LSL \geq k$

1.1.2.2. For one-sided tolerance limit – upper specification: $Z.USL \geq k$

Two-sided tolerance limit sampling plans use the following acceptance criteria for a Milford site manufacturing process to be considered validated:

1.1.2.3. Standard Deviation $\leq$ Maximum Standard Deviation (MSD),
 $Z.LSL \geq k$ and $Z.USL \geq k$

2. CALCULATING ACCEPTANCE CRITERIA VALUES

2.1. The process to calculate standard deviation, Z.LSL, and Z.USL; and how to determine the corresponding maximum standard deviation is defined below.

2.1.1. Standard deviation is calculated from the test data, as follows:

2.1.1.1. Calculate the Mean (the simple average) of the data values for the specification.

2.1.1.2. For each data value subtract the Mean and square the result.

2.1.1.3. Sum the values from Step 2.1.1.2.

2.1.1.4. Divide by the number of Samples minus one (n-1).

2.1.1.5. Take the square root of the value from 2.1.1.4.

2.1.1.6. The formula for Standard Deviation is provided below:

$s = \sqrt{\frac{\sum(x - \bar{x})^2}{n - 1}}$	s = Standard Deviation n = Total number of samples tested $\bar{x}$ = Sample mean x = individual data values Σ = Sigma (sum of...)
--	--

2.1.2. The Z.LSL is calculated using the following formula:

$$Z.LSL = \frac{\text{Test Data Mean} - \text{Lower Test Specification}}{\text{Test Data Standard Deviation}}$$

2.1.3. The Z.USL is calculated using the following formula:

$$Z.USL = \frac{\text{Upper Test Specification} - \text{Test Data Mean}}{\text{Test Data Standard Deviation}}$$

Process Validation Procedure

Document # 730001835

Version # 08

Page 15 of 17

2.1.4. The Maximum Standard Deviation (MSD) shall be calculated, using the following formula:

$$MSD = \frac{\text{Upper Test Specification} - \text{Lower Test Specification}}{2 * Z_{p^{**}}}$$

To determine $Z_{p^{**}}$ Minitab finds the upper tail area from the standard normal distribution, known as p^* , corresponding to the lowest k value. The p^* value is then divided by two (2) and Minitab then finds the associated upper tail area, which is $Z_{p^{**}}$.

2.1.4.1. To determine $Z_{p^{**}}$ manually, find the p^* value equal to the lowest k value, (as provided in the Risk-Based Statistical Criteria for Process Validation Table in Section 8.9.2.3.) from the Table in Appendix C.

2.1.4.1.1. The p^* value is found by finding the first two (2) numbers of the k value in the first column and then the closest decimal values from the header row.

- For example, a sampling plan defined by a 90% confidence has a lowest k value of 1.73910.
- Find the row with 1.7 at the left, and then the column with .04 at the top to get the p^* value of .0409 where they intercept (Highlighted in yellow with bolded numbers).
- Divide .0409 by two (2) to get 0.02045.
- Find the closest value to 0.02045 within the table, which is .02068. This is found in the fifth column. (Highlighted in yellow)
- From the value of .02068 find the corresponding value from the first column/row of 2.04 which is $Z_{p^{**}}$.

Process Validation Procedure

Document # 730001835

Version # 08

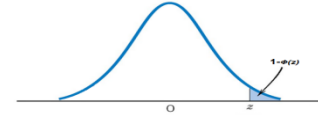
Page 16 of 17

APPENDIX C

1. AREAS IN UPPER TAIL OF THE NORMAL DISTRIBUTION TABLE

1.1. The function tabulated is $1 - \Phi(z)$ where $\Phi(z)$ is the cumulative distribution function of a standard Normal variable, z .

1.2. Thus $1 - \Phi(z) = \frac{1}{\sqrt{2\pi}} \int_z^{\infty} e^{-z^2/2}$ is the probability that a standardized Normal variate selected at random will be greater than a value of $z \left(= \frac{x - \mu}{\sigma} \right)$.



$\frac{x - \mu}{\sigma}$	.00	.01	.02	.03	.04	.05	.06	.07	.08	.09
0.0	0.5000	0.4960	0.4920	0.4880	0.4840	0.4801	0.4761	0.4721	0.4681	0.4641
0.1	0.4602	0.4562	0.4522	0.4483	0.4443	0.4404	0.4364	0.4325	0.4286	0.4247
0.2	0.4207	0.4168	0.4129	0.4090	0.4052	0.4013	0.3974	0.3936	0.3897	0.3859
0.3	0.3821	0.3783	0.3745	0.3707	0.3669	0.3632	0.3594	0.3557	0.3520	0.3483
0.4	0.3446	0.3409	0.3372	0.3336	0.3300	0.3264	0.3228	0.3192	0.3156	0.3121
0.5	0.3085	0.3050	0.3015	0.2981	0.2946	0.2912	0.2877	0.2843	0.2810	0.2776
0.6	0.2743	0.2709	0.2676	0.2643	0.2611	0.2578	0.2546	0.2514	0.2483	0.2451
0.7	0.2420	0.2389	0.2358	0.2327	0.2296	0.2266	0.2236	0.2206	0.2177	0.2148
0.8	0.2119	0.2090	0.2061	0.2033	0.2005	0.1977	0.1949	0.1922	0.1894	0.1867
0.9	0.1841	0.1814	0.1788	0.1762	0.1736	0.1711	0.1685	0.1660	0.1635	0.1611
1.0	0.1587	0.1562	0.1539	0.1515	0.1492	0.1469	0.1446	0.1423	0.1401	0.1379
1.1	0.1357	0.1335	0.1314	0.1292	0.1271	0.1251	0.1230	0.1210	0.1190	0.1170
1.2	0.1151	0.1131	0.1112	0.1093	0.1075	0.1056	0.1038	0.1020	0.1003	0.0985
1.3	0.0968	0.0951	0.0934	0.0918	0.0901	0.0885	0.0869	0.0853	0.0838	0.0823
1.4	0.0808	0.0793	0.0778	0.0764	0.0749	0.0735	0.0721	0.0708	0.0694	0.0681
1.5	0.0668	0.0655	0.0643	0.0630	0.0618	0.0606	0.0594	0.0582	0.0571	0.0559
1.6	0.0548	0.0537	0.0526	0.0516	0.0505	0.0495	0.0485	0.0475	0.0465	0.0455
1.7	0.0446	0.0436	0.0427	0.0418	0.0409	0.0401	0.0392	0.0384	0.0375	0.0367
1.8	0.0359	0.0351	0.0344	0.0336	0.0329	0.0322	0.0314	0.0307	0.0301	0.0294
1.9	0.0287	0.0281	0.0274	0.0268	0.0262	0.0256	0.0250	0.0244	0.0239	0.0233
2.0	0.0227	0.0222	0.0216	0.0211	0.0206	0.0201	0.0197	0.0192	0.0187	0.0183
2.1	0.0178	0.0174	0.0170	0.0165	0.0161	0.0157	0.0153	0.0150	0.0146	0.0142
2.2	0.0139	0.0135	0.0132	0.0128	0.0125	0.0122	0.0119	0.0116	0.0113	0.0110
2.3	0.0107	0.0104	0.0101	0.0099	0.0096	0.0093	0.0091	0.0088	0.0086	0.0084
2.4	0.0082	0.0079	0.0077	0.0075	0.0073	0.0071	0.0069	0.0067	0.0065	0.0063
2.5	0.0062	0.0060	0.0058	0.0057	0.0055	0.0053	0.0052	0.0050	0.0049	0.0048
2.6	0.0046	0.0045	0.0044	0.0042	0.0041	0.0040	0.0039	0.0037	0.0036	0.0035
2.7	0.0034	0.0033	0.0032	0.0031	0.0030	0.0029	0.0028	0.0028	0.0027	0.0026
2.8	0.0025	0.0024	0.0024	0.0023	0.0022	0.0021	0.0021	0.0020	0.0019	0.0019
2.9	0.0018	0.0018	0.0017	0.0016	0.0016	0.0015	0.0015	0.0014	0.0014	0.0013
3.0	0.0013	0.0013	0.0012	0.0012	0.0011	0.0011	0.0011	0.0010	0.0010	0.0010
3.1	0.0009	0.0009	0.0009	0.0008	0.0008	0.0008	0.0007	0.0007	0.0007	0.0007
3.2	0.0006	0.0006	0.0006	0.0006	0.0006	0.0005	0.0005	0.0005	0.0005	0.0005
3.3	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004	0.0003	0.0003	0.0003	0.0003
3.4	0.0003	0.0003	0.0003	0.0003	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
3.5	0.0002	0.0002	0.0002	0.0002	0.0002	0.0001	0.0001	0.0001	0.0001	0.0001
3.6	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
3.7	0.0001	0.0001	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
3.8	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Process Validation Procedure

Document # 730001835

Version # 08

Page 17 of 17

DOCUMENT HISTORY

(Note: Complete Document History may be obtained via the Document Management System.)

VERSION:	08	ORIGINATOR:	James J. Stors	Change ID:	N/A
SUMMARY OF CHANGE: Updated the Scope section/document to include Singapore and LC product support sites. Changed "Performer" to "Executor" and "Validation Engineering" to "VMP Coordinator" in Section 4. Removed all references to the Validation Master Plan Procedure, 730002232. Added the requirements from the Validation Master Plan Procedure, that will continue to apply, to Section 8.2. Added the re-executed IQ approval authority to Section 8.4. Added Analytical Test Method to Sections 3 and 8.5.					

VERSION:	07	ORIGINATOR:	James J. Stors	Change ID:	N/A
SUMMARY OF CHANGE: Updated Section 6.1 to define executed individual station Quality Document DIR naming. ADDED Validation Master Plan Procedure 730002232 reference to Section 8.1. Removed duplicate systems from the Medium Risk Level of the Validation Assessment Form Section 8.2.2.1. Moved Process Flow Chart to the Appendix Section. (NOTE VERSION 06 ABANDONED)					

VERSION:	06	ORIGINATOR:	James J. Stors	Change ID:	N/A
SUMMARY OF CHANGE: Abandoned					

VERSION:	05	ORIGINATOR:	James J. Stors	Change ID:	N/A
SUMMARY OF CHANGE: Revised the procedure per the Waters Global Validation Policy, 730000837.					