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## Process validation in medical devices

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## Guideline Contributors

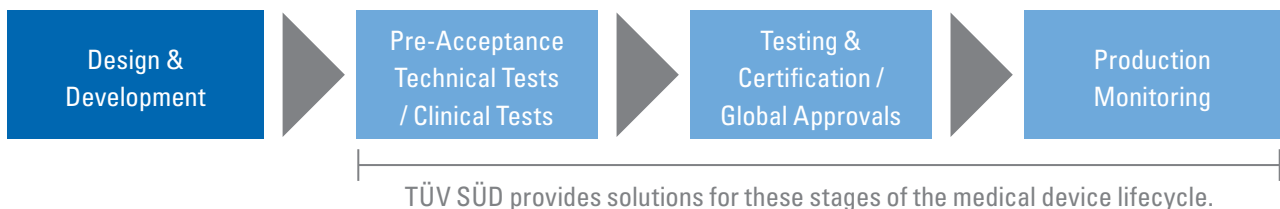
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# Introduction

## Guideline on process validation activities

International regulations for medical devices [1, 2, 3, 4] stipulate validation of manufacturing processes for medical devices, where the resulting process output cannot be or is not verified by subsequent monitoring or measurement. This entails activities that are not only limited to the validation of the manufacturing process itself but may also include equipment qualification, computer system validation and test method validation.

When carrying out process validation activities, additional points to consider include statistical sampling plans, process monitoring, validation change control and good documentation practice. Manufacturers of medical devices should also note that the requirements on process validations are not limited to their own premises but also apply to processes conducted offsite by suppliers. This guideline supports manufacturers of medical devices in fulfilling these regulatory requirements.

### Standards and regulations

This guideline is based on the following standards and regulations:

- [1] ISO 13485:2016
- [2] 21CFR820
- [3] GHTF/SG3/N99-10:2004 (Ed.2)
- [4] ZLG 3.9 B18
- [5] Final Guidance for Industry and FDA Staff, General Principles of Software Validation

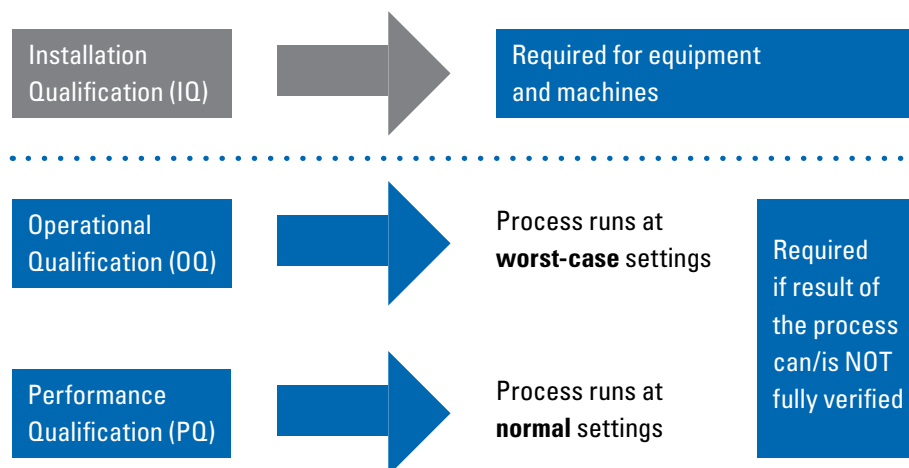


# Validation planning

## Guarantee a predictable outcome

The Global Harmonization Task Force (GHTF) [3] defines process validation as 'a term used in the medical device industry to indicate that a process has been subject to such scrutiny that the result of the process ... can be practically guaranteed'. Prior to undertaking any validation activities, thorough planning is essential. Validation will include Installation Qualification (IQ) for equipment and machines, as well as Operational Qualification (OQ) and Performance Qualification (PQ) for the manufacturing process. It must be emphasised that additional process- and/or product-specific requirements are to be considered. This includes but is not limited to sterilisation and sterile packaging processes where PQ also includes challenging of process tolerances and limits.

## Typical elements of process validation



Documented procedures describing the approach for process validation are a requirement [1, 2]. Beyond listing the definitions used, this documentation should describe responsibilities and delineate authorities. The different elements of process validation and the sequence of execution are to be clarified, including requirements for re-validation. Procedures for process validation should also contain further details regarding testing, training, documentation, review and approval.



## Validation Master Plan

Manufacturers often choose to develop a Validation Master Plan (VMP) as a tool to control and monitor the status of validation activities. As VMPs are not required by regulations, the content and structure can vary widely.

The elements typically found in a VMP include listings and references to the qualifications and validations performed internally and externally at suppliers, as well as schedules for re-validation activities. VMPs can be used to demonstrate management

commitment to validation activities. They also support the planning and allocation of human and financial resources, as requested by regulations [1, 2, 4].

## Individual validation plan

An individual validation plan is another tool that is widely used to support the planning for more complex projects such as new manufacturing lines or production transfers. The individual

validation plan may establish a generic validation strategy and offer the potential to approach validation activities in a more structured manner. Product matrix approaches

(bracketing or grouping of products), combined protocols and reports may also be described and justified in an individual validation plan.



# Installation Qualification

## Ensure reliable operation of equipment

Installation Qualification (IQ) is defined by GHTF as 'establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendations of the supplier of the equipment are suitably considered' [3]. Also referred to as equipment qualification [1], IQ is regarded as an appropriate method to fulfil regulatory requirements.

All equipment and machines used in the manufacturing process of medical devices require IQ. It supports manufacturers in properly establishing key areas of operation such as maintenance plans, calibration tolerances and intervals, as well as cleaning

or microbiological procedures. Recommendations or instructions from third-party equipment suppliers are an essential source of information and must be considered during installation activities.

Applicable support systems and utilities must also be verified and completed during installation. This extends beyond the supply of electricity and compressed air to encompass other topics such as material supply or data transfer infrastructure. Functional testing of the equipment, including alarm and control systems, must also be carried out. Furthermore, operating instructions for the equipment and training documentation needs to be prepared accordingly. Any documentation such as manuals,

drawings or codes that are needed to operate, maintain or repair the equipment should be compiled and retained for future use.

IQ adds value for manufacturers by helping to prevent future issues. When done properly, it ensures that equipment operates in a reliable and predictable manner. Successful completion of the IQ is usually a prerequisite to continue process validation within the Operational Qualification.

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**IQ adds value for manufacturers by helping to prevent future issues.**

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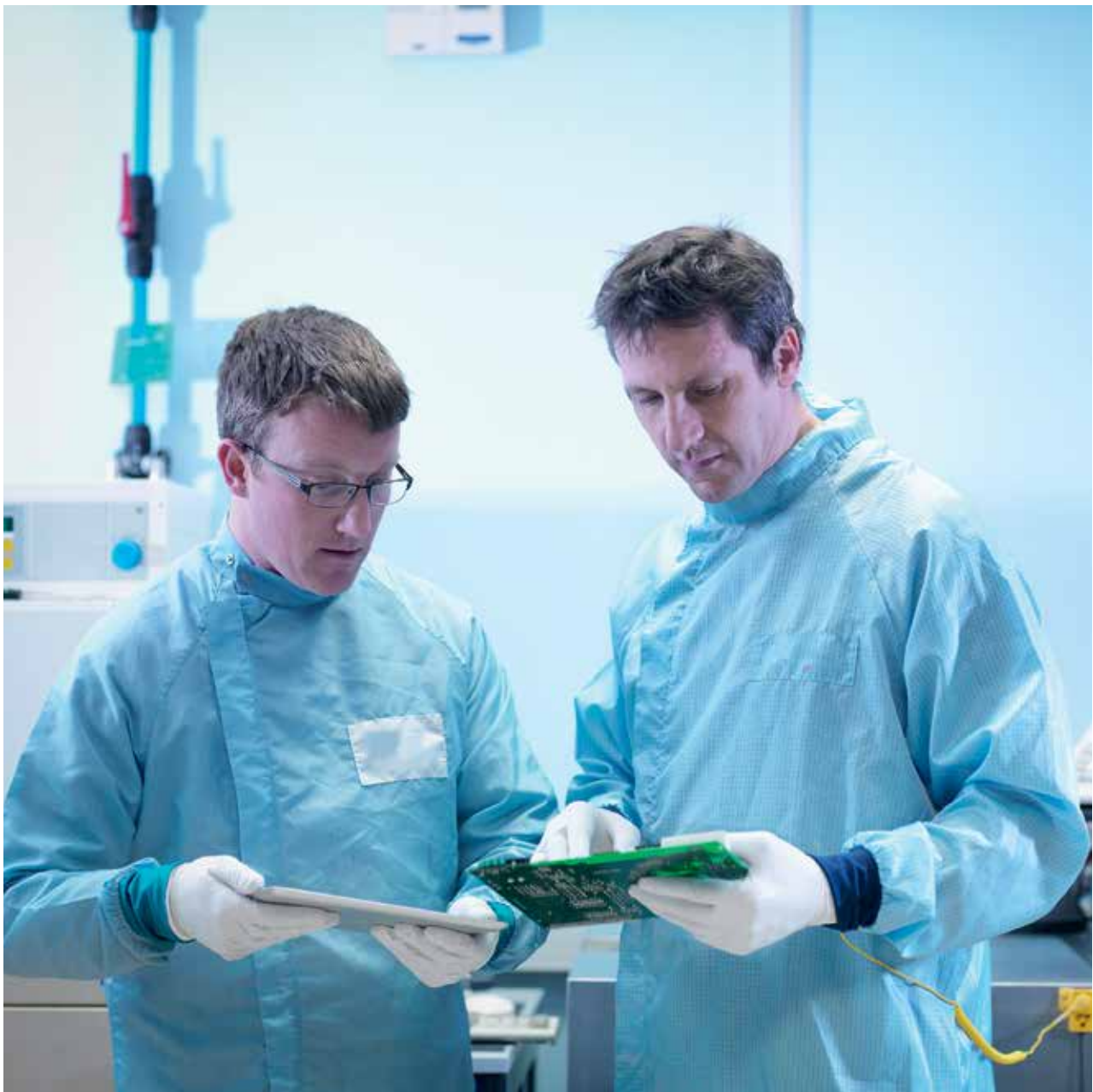


## Computer system validation

Today, virtually all manufacturing equipment is controlled by computerised systems such as programmable logic controls or computers. Additional software tools are also used to transfer or evaluate process data. Validation is needed to provide objective evidence that

these computerised systems and software tools are suitable for their intended purpose [1, 2, 5]. IQ/OQ/PQ terminology may be used for computer system validation, however it is acknowledged that software professionals may apply different terms [5].

If a computerised system is used in connection with the manufacturing equipment, computer system validation must be successfully completed before IQ can be approved.





# Operational Qualification

Meet all predetermined requirements at process limits

GHTF defines Operational Qualification (OQ) as 'establishing by objective evidence process control limits and action levels which result in product that meets all predetermined requirements' [3]. An OQ is usually accomplished in two main steps:

1. Identification of critical process parameters
2. Provision of evidence that production at worst-case settings will still result in a product that meets specifications

With regard to the first step, Design of Experiments (DoE) is a widely used tool for identifying critical process parameters. Manufacturers

may choose to incorporate this essential process during developmental work in separate documentation packages prior to OQ. Alternatively, DoE can feature directly in OQ protocols. Both pathways are possible as long as the goal of understanding the process and its parameters is achieved and demonstrated.

The second step, providing evidence that a product will meet pre-determined requirements, necessitates statistically sound sampling plans and valid test methods. Proper product acceptance criteria are key to successful validation. OQ samples are produced

at the established process limits and adequate process documentation is retained. Once OQ samples are tested, results are recorded and evaluated thoroughly, including statistical analyses. In most cases, OQ should be successfully completed as a prerequisite before starting Performance Qualification.

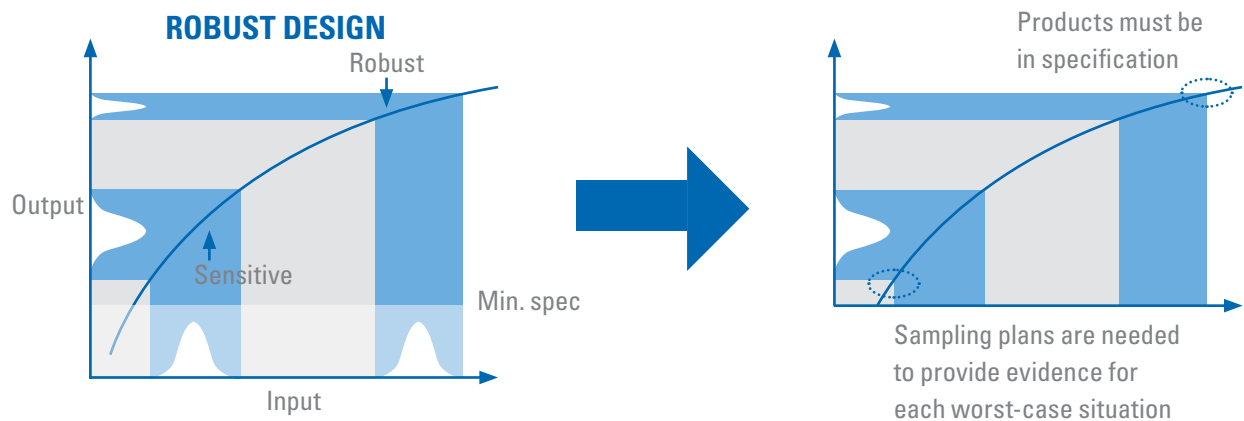
**OQ samples are produced at the established process limits.**



## Basics of Operational Qualification

### Scope of the OQ

- Identification of critical process parameters
- Evidence that product in specification will be produced at worst-case settings



GHTF Study Group 3 – Quality Management Systems  
Process Validation Guidance – January 2004



# Performance Qualification

## Manufacture with consistency

Following the GHTF Guidance [3], Performance Qualification (PQ) can be defined as 'establishing by objective evidence that the process, under anticipated conditions, consistently produces a product that meets all predetermined requirements'. In order to determine the scope, range and size of the PQ, it is vital to understand the natural process variability and other

influences that routine manufacturing may be exposed to.

The PQ plan should clearly describe how many routine manufacturing runs are required to show repeatability and stability of the processes under consideration. Additionally, sampling plans need statistically sound justifications. For example, consideration should

be given to the number of different pieces of equipment used, variations in machine set-up, different raw material or component batches, working in shifts, environmental conditions or degradation of tooling.

Successful completion of the PQ will enable the manufacturer to initiate approval of the new or changed manufacturing process.

## Process monitoring

Once the manufacturing process has been validated, it is a requirement to maintain the validated state. This entails monitoring and controlling validated process parameters to ensure that the specified requirements continue to be met [2, 3]. Quality control charts, also known as Statistical Process Control (SPC), are one of the tools commonly used for this purpose.

This involves establishing action and warning limits then determining rules for atypical process behaviour.

Automated alarm and control systems (if qualified) may also be used to control validated process parameters.

Detecting negative trends or unexpected shifts of the process is key, which necessitates thorough and timely data analysis. In the event that these shifts or trends are detected, re-validation, investigations and/or corrective actions may be needed. Re-validation should also be considered if deficiencies are

identified in the processes. This includes but is not limited to recalls, complaints, internal and external audit trends, failure investigation, Corrective and Preventive Action (CAPA), equipment significant maintenance or corrective maintenance trends.

For specific processes such as sterilisation, re-validation is scheduled in defined intervals in compliance with applicable standards and regulations [1, 2, 4].

## Validation change control

Documented procedures including criteria for re-validation and approval of changes to processes or qualified equipment must be implemented [1, 2, 3, 4]. The impact of changes is evaluated and considered when

determining the extent of re-validation activities needed. Complete re-validation will be triggered by significant changes such as the implementation of new manufacturing technologies or

production line transfers. Simpler events including changes within validated limits may require less extensive re-validation activities.



## Good documentation practice

Qualification and validation records must be maintained to demonstrate conformance to specified requirements and the effective operation of the qualified equipment and validated process. These records must contain appropriate references when supporting records

are maintained separately from the qualification or validation package.

Validation records contain the names and signatures of the individual(s) preparing, reviewing and approving plans and reports. Process parameters used during

manufacturing of OQ or PQ samples are also documented. In addition, raw data generated through testing is recorded, including the identification of test persons and the equipment used as well as the calibration status.



# Statistical sampling plans

## Select the optimal approach

The application of statistically sound sampling plans is a requirement [1, 2, 3, 4] and was recently reinforced [1]. For harmonised standards and/or applicable regulations, medical device specific requirements for statistical approaches may need to be selected. In all cases, manufacturers are responsible for determining and justifying statistically sound sampling plans.

When it comes to determining such sampling plans, there are a variety of statistical approaches and methodologies to consider. Manufacturers often use the principles of the Accepted Quality Limit (AQL) and the Rejected Quality Limit (RQL), also called Limiting

Quality (LQ), as defined in ISO 3534-2:2006.

AQL defines the level of quality a sampling plan usually accepts with a high level of probability. Applicable standards for AQL-based sampling plans are:

- ISO 2859-1 Sampling inspection by attributes
- ANSI/ASQ Z1.4 Sampling procedures and tables for inspection by attributes
- ISO 3951-1 Sampling inspection by variables
- ANSI/ASQ Z1.9 Sampling procedures and tables for inspection by variables

Note that skip-lot sampling plans as per ISO 2859-3 cannot be used for critical classes of nonconforming items or nonconformities.

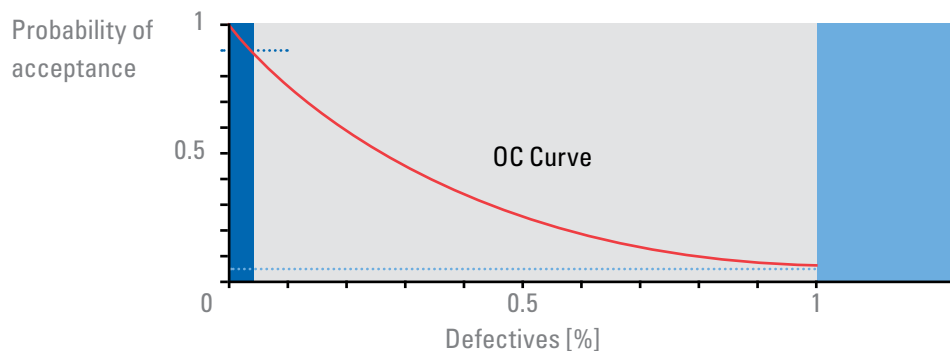
RQL defines the level of quality a sampling plan usually rejects with a high level of probability. Current versions of ISO 2859-1, ISO 2859-2 and ISO 3951-1 include tables for consumer's risk (RQL, LQ) as well.

Both AQL and RQL can be found on the Operating Characteristic Curve (OC-Curve) of the sampling plan. The OC-Curve shows the relationship between the probability of a product's acceptance and the incoming quality level for a given sampling plan.

## AQL versus RQL with an example of an OC-Curve

AQL defines the level of quality the sampling plan routinely accepts (producer's risk).

LTPD (RQL, LQ, UQL) defines the level of quality the sampling plan routinely rejects (consumer's risk).



## Accepted Quality Limit versus Rejected Quality Limit

The concept of AQL is based on a well-known process and is not the optimal measure for patient safety if the correlating customer risk is not known and justified. AQL-based sampling plans are usually applied in routine manufacturing after process reliability is established.

For this reason, an RQL-based sampling plan offers a more suitable approach for process validation, as it more accurately predicts the amount of defective products delivered to the customer.

### A RQL-based sampling plan offers a more suitable approach for process validation.

ISO 16269-6 is another applicable standard that is often used for medical devices. This standard introduces the method of statistical tolerance intervals and is also based on consumer risk. Therefore, ISO 16269-6 is suitable for statistical sampling plans in process validation. A statistical tolerance interval depends on a confidence level and a stated proportion of the sample group. Once the confidence level and the proportion targeted is known, the standard will lead to sample sizes for both variable and attribute data.

The differentiation of attributive test results versus variable test results is an additional consideration when generating statistical sampling plans. Examples for attributive data sets include criteria such as go/no-go, good/bad, leaking/tight, particle/particle-free.

Test methods using attributive acceptance criteria may be easy to implement and less expensive. However, attributive sampling plans result in higher sample sizes than variable sets of data.

Variable data is a set of continuous measurements, ideally normally distributed. By enabling statistical evaluations, it delivers greater knowledge than attributive data. Done correctly, variable sampling plans result in lower sample sizes than attributive sampling plans. The advantage of having lower sample sizes necessitates statistical calculations and evaluations as given by the standards. Using variable sampling plans without doing the statistical calculation is insufficient.

### Statistical sampling plans in summary

- AQL-based sampling plans are focussed on producer's risk. Using these plans during process validation is not recommended unless the referring RQL is justified.
- RQL-based sampling plans are focussed on consumer's risk. Using these plans during process validation is recommended. Selection of RQLs and confidence levels is to be justified.
- ISO 16269-6 includes sampling plans for both variable and attribute data.

It must be emphasised that the application of statistical sampling plans is required. However, these plans will not replace proper process development or monitoring of critical process parameters. Technical understanding of the manufacturing processes is key to ensure that the process results 'can be practically guaranteed' as stated at the beginning of this guideline.

**Technical understanding of the manufacturing processes is key to ensure that the process results 'can be practically guaranteed' as stated at the beginning of this guideline.**



## GLOSSARY OF ACRONYMS

AQL – Accepted Quality Limit	OC-CURVE – Operating Characteristic Curve
CAPA – Corrective and Preventive Action	OO – Operational Qualification
DoE – Design of Experiments	PQ – Performance Qualification
GHTF – Global Harmonization Task Force	RQL – Rejected Quality Limit
IQ – Installation Qualification	SPC – Statistical Process Control
LQ – Limiting Quality	UQL – Unacceptable Quality Level
LTPD – Lot Tolerance Percent Defective	VMP – Validation Master Plan

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