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Medicinal Products – Quality, Safety and Efficacy

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EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines for Good Manufacturing Practice
for Medicinal Products for Human and Veterinary Use

Annex 15: Qualification and Validation

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: Revision 1

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Draft guideline discussion with other groups	June – September 2013
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Re-discussion in GMDP IWG	September 2014
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Reasons for changes: Update as per concept paper on revision of Annex 15.

Summary of changes: This change to annex 15 takes into account changes to other sections of the EU-GMP Guide Part I, Annex 11, ICH Q8, Q9, Q10 and Q11, QWP guidance on process validation and changes in manufacturing technology.

Deadline for coming into operation: to be determined.

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QUALIFICATION AND VALIDATION

Principle

This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products. It is a GMP requirement that manufacturer's control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed. Computerised systems used for the manufacture of medicinal products should be validated according to the requirements of Annex 11. The relevant concepts and guidance presented in ICH Q8, Q10 and Q11 should also be taken into account.

General

A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of validation and qualification should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes. The principles in ICH Q8, Q9, Q10 and Q11 or other systems guaranteeing at least the same level of product quality and security should be used to support validation and qualification activities.
Data supporting qualification and/or validation studies which were obtained from sources outside of the manufacturers own validation programme may be used provided that this approach has been justified and that there is adequate assurance that controls were in place throughout the acquisition of such data.

1. ORGANISING AND PLANNING FOR QUALIFICATION AND VALIDATION

1.1 All qualification and validation activities should be planned and take the life cycle of equipment, process and product into consideration.

1.2 Validation activities should only be performed by suitably trained personnel who follow approved validation procedures.

1.3 Validation personnel should report as defined in the pharmaceutical quality system although this may not necessarily be to a quality management or a quality assurance function, however there should be appropriate oversight over the whole validation life cycle.

1.4 The key elements of the site validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent document.

1.5 The VMP should be a summary document which is brief, concise, clear and contain data on at least the following:

a) Validation policy.

b) The organisational structure for validation activities.

c) Summary of the facilities, systems, equipment, processes on site and the current validation status.

d) Template formats to be used for protocols and reports.

e) Planning and scheduling.

f) Change control and deviation management for validation.

g) Handling of acceptance criteria

h) References to existing documents.

i) An assessment of the resources required.

j) The ongoing validation strategy, including revalidation and / requalification, where applicable.

k) Confirmation that the materials used for validation are of the required quality and suppliers are qualified to the appropriate level. .

1.6 For large and complex projects, planning takes on added importance and it may be necessary to create a separate VMP.

1.7 A quality risk management approach should be used for validation activities with risk assessments repeated, as required, in light of increased knowledge and understanding from any changes during the project phase or during commercial production. The way in which risk assessments are used to support validation activity should be clearly documented.

2. DOCUMENTATION INCLUDING VMP

2.1 Good documentation practices are important to support knowledge management throughout the validation lifecycle.

2.2 All documents generated during validation should be approved and authorised by appropriate personnel as defined in the pharmaceutical quality system.

2.3 The relationship between documents in complex validation projects should be clearly defined and any inter-relationships documented.

2.4 A written validation protocol should be prepared which defines the critical systems, attributes and parameters which are important and the acceptance criteria for each.

2.5 Where validation protocols are supplied by a third party, the manufacturer should confirm suitability and compliance with company procedures before approval.

2.6 Any changes to the approved protocol during execution should be documented as a deviation and be scientifically justified.

2.7 Results which fail to meet the pre-defined acceptance criteria should be recorded as a deviation, be fully investigated and any implications for the validation discussed in the report.

2.8 The conclusions of the validation should be reported and the results obtained summarised against the acceptance criteria. Any subsequent changes to acceptance criteria should be scientifically justified and a final recommendation made as to the outcome of the validation.

2.9 A formal release for the next step in the validation process should be authorised by the relevant responsible personnel either as part of the validation report approval or as a

separate summary document. Conditional approval to proceed to the next stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.

3. QUALIFICATION STAGES FOR EQUIPMENT, FACILITIES AND UTILITIES

3.1 Validation and qualification activities should consider all stages from initial development of the user requirements specification or initial process development through to the end of use of the equipment, facility or process. The main stages and some suggested criteria (although this depends on individual project circumstances and may be different) which could be included in each stage are indicated below:

User requirements specification (URS)

3.2 The specification for new facilities, systems or equipment should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks minimised. The URS should be a point of reference throughout the validation life cycle.

Design qualification (DQ)

3.3 The next element in the validation of new facilities, systems or equipment is DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should also be verified during the design qualification.

Factory acceptance testing (FAT) /Site acceptance testing (SAT)

3.4 Equipment, especially if incorporating novel or complex technology, should be evaluated at the vendor prior to delivery.

3.5 Prior to installation, equipment should be confirmed to comply with the URS/ functional specification at the vendor site unless otherwise justified.

3.6 Where appropriate and justified, documentation review and some tests could be performed at the FAT stage without the need to repeat on site if it can be shown that the functionality is not affected by the transport and installation.

3.7 FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.

Installation qualification (IQ)

3.8 IQ should be performed on new or modified facilities, systems and equipment.

3.9 IQ could include, but is not be limited to the following:

a) Installation of equipment, pipe work, services and instrumentation as detailed in the design and confirmation of current engineering regarding drawings and specifications.

b) Verification of the correct installation against pre-defined criteria.

c) Collection and collation of supplier operating and working instructions and maintenance requirements.

d) Calibration of instrumentation.

e) Verification of the materials of construction.

Operational qualification (OQ)

3.10 OQ normally follows IQ but depending on the complexity of the equipment it may be performed as a combined Installation/Operation Qualification (IOQ).

OQ could include but is not be limited to the following:

a) Tests that have been developed from the knowledge of processes, systems and equipment.
b) Tests to confirm upper and lower operating limits, and /or "worst case" conditions.

3.11 The completion of a successful OQ should allow the finalisation of maintenance plans, standard operating and cleaning procedures, operator training and preventative maintenance requirements.

Performance qualification (PQ)

3.12 PQ should follow the successful completion of IQ and OQ.

3.13 Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ or Process Validation.

3.14 PQ could include, but is not be limited to the following:

a) Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions with worst case batch sizes. The frequency of sampling used to confirm process control should be justified.

b) Tests should cover the operating range of the intended process, unless documented evidence from the development phases which confirm the operational ranges are available.

4. PROCESS VALIDATION

General

4.1 The requirements and principles outlined in this section are applicable to the manufacture of all pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes, site transfers and ongoing process verification.

4.2 This section should be used in conjunction with the current EMA guideline on Process Validation. Note: It should be taken into account that the guideline on Process Validation is intended to provide guidance on the information and data to be provided in

the regulatory submission and GMP requirements extend beyond this. It should also be noted that a lifecycle approach is applied linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.

4.3 Medicinal products may be developed using a traditional approach or a continuous verification approach however irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market. Manufacturing processes should undergo a prospective validation programme wherever possible prior to marketing of the product.

4.4 Process validation for new products should cover all intended marketed strengths and sites of manufacture, however for products which are transferred from one site to another or within the same site, and where there is existing product knowledge, including the content of the previous validation, the number of validation batches could be reduced by the use of a bracketing approach. This approach could be acceptable for different strengths, batch sizes and pack sizes/ container types if justified.

4.5 For the site transfer of legacy products, the manufacturing process and controls should comply with the Marketing Authorisation and meet current expected licensing standards for that product type. If necessary, variations to the Marketing Authorisation should be submitted.

4.6 Process validation should establish whether all quality attributes and process parameters which are considered important for ensuring the validated state and acceptable product quality can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities.

4. 7 Normally batches manufactured for process validation should be the same size as the intended commercial scale batches and the use of any other batch sizes should be justified. e.g. for a continuous manufacturing process.

4.8 Facilities, systems, utilities and equipment used for process validation should be qualified and test methods should be validated.

4.9 For all products irrespective of the approach used, process knowledge from development studies should be accessible to the manufacturing site, unless otherwise justified, and be the basis for validation activities.

4.10 For process validation batches, production, development, or other site transfer personnel may be involved. Batches should only be manufactured by trained personnel in accordance with GMP using approved documentation. It is expected that production personnel are involved in the manufacture of validation batches to facilitate product understanding when commercial manufacture starts.

4.11 The suppliers of critical starting and packaging materials should be qualified prior to the manufacture of validation batches; otherwise a justification based on the application of quality risk management principles should be documented.

4.12 It is especially important that the underlying process knowledge for the design space justification (if used), and for development of any mathematical models used to confirm a state of control should be available.

4.13 Where validation batches are released to the market this should be pre-defined. The conditions under which they are produced should fully comply with GMP, with the validation acceptance criteria, with any continuous process verification criteria (if used) and with the Marketing Authorisation.

Concurrent validation

4.14 In exceptional circumstances where there is a strong risk – benefit to the patient, it may be acceptable not to complete a validation programme before routine production starts and concurrent validation could be used. However, the decision to carry out concurrent validation must be justified, documented in the VMP and approved by authorised personnel.

4.15 Where a concurrent validation approach has been adopted, there should be sufficient data to support a conclusion that any given batch of product is uniform and meets the defined acceptance criteria. The results and conclusion should be formally documented and available to the Qualified Person prior to certification of the batch.

Traditional approach to validation

4.16 In the traditional approach, a number of batches of the finished product are manufactured under routine conditions to confirm reproducibility.

4.17 The number of batches manufactured and the number of samples taken should be based on quality risk management principles, allow the normal range of variation and trends to be established and provide sufficient data for evaluation. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.

4.18 Without prejudice to 4.17, it is generally considered acceptable that a minimum of three consecutive batches would constitute a validation of the process although an alternative number of batches may be justified taking into account whether standard methods of manufacture are used and whether similar products or processes are already used at the site. An initial validation exercise with three batches may need to be supplemented with further data obtained from subsequent batches as part of an on-going process verification exercise.

4.19 A process validation protocol should be prepared which defines the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on development data or documented process knowledge.

4.20 Validation protocols should include, but are not be limited to the following:

a) A short description of the process.
b) Summary of the CQA’s to be investigated
c) Summary of CPP’s and their associated limits.

d) Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion.

e) List of the equipment/facilities to be used (including measuring/

f) monitoring/recording equipment) together with the calibration status.

g) List of analytical methods and method validation, as appropriate.

h) Proposed in-process controls with acceptance criteria and the reason(s) which each in-process control is selected.

i) Additional testing to be carried out, with acceptance criteria.

j) Sampling plan and the rationale behind it.

k) Methods for recording and evaluating results.

l) Process for release and certification of batches (if applicable).

m) Functions and responsibilities.

n) Proposed timetable.

Continuous process verification

4.21 For products developed by a quality by design approach, where it has been scientifically established that routine process control provides a high degree of assurance of product quality, then continuous process verification can be used as an alternative to traditional process validation.

4.22 The process verification system should be defined and there should be a science based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation. This should also include regular evaluation of the control strategy. Process Analytical Technology and multivariate statistical process control may be used as tools. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.

4.23 The general principles in 4.1 – 4.15 above still apply.

4.24 A hybrid approach using the traditional approach and continuous process verification for different production steps can also be used. Where there is a substantial amount of product and process knowledge and understanding which has been gained from manufacturing experience and historical batch data, continuous verification may also be used for any validation activities after changes or during ongoing process verification even though the product was initially validated using a traditional approach.

Ongoing Process Verification during Lifecycle

4.25 Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.

4.26 The extent and frequency of ongoing process verification should be reviewed periodically and modified if appropriate, considering the level of process understanding and process performance at any point in time in the product lifecycle.

4.27 On going process verification should be conducted under an approved protocol and a corresponding report should be prepared to document the results obtained. Statistical tools should be used, where appropriate, to support any conclusions with regard to the variability and capability of a given process and ensure a state of control.

4.28 On going process verification should be used to support the validated status of the product in the Product Quality Review, however, incremental changes over time should also be considered and the need for any additional actions (e.g. enhanced sampling) should be assessed.

4.29 On going process verification should be considered where any individual change or successive incremental changes during the product lifecycle could have an impact on the validated status of the process.

5. VERIFICATION OF TRANSPORTATION

5.1 Finished medicinal products, investigational medicinal products, bulk product and samples should be transported in accordance with the conditions defined in the Marketing Authorisation, product specification file or by the manufacturer.

5.2 It is recognised that validation of transportation may be challenging due to the variable factors involved however transportation routes should be clearly defined. For transport across continents seasonal variations should also be considered.

5.3 A risk assessment should be performed to consider the impact of conditions other than temperature during transportation e.g. humidity, vibration, handling, delays during transportation, failure of data-loggers, topping up liquid Nitrogen, product susceptibility and any other relevant factors.

5.4 Due to the variable conditions expected during transport e.g. delays at airports, continuous monitoring of any critical environmental conditions to which the product may be subjected should be performed.

6. VALIDATION OF PACKAGING

6.1 Variation in equipment processing parameters during primary packaging may have a significant impact of the integrity and correct functioning of the pack (e.g. blister strips, sachets and sterile components) therefore primary packaging processes should undergo validation.

6.2 Qualification of the machine settings for the types of pack above should be carried out at the minimum and maximum operating ranges defined for the critical components parameters such as temperature, machine speed and sealing pressure or for any other factors.

7. VALIDATION OF UTILITIES

7.1 The quality of steam, water, air, other inert gases, coolants etc. should be confirmed following installation using the qualification steps described in section 3.

7.2 The period and extent of qualification should also reflect any seasonal variations, if applicable, and the intended use of the utility.

7.3 A risk assessment should be carried out where there may be direct contact with the product e.g. HVAC systems or indirect contact such as through heat exchangers to mitigate any risks of failure.

8. VALIDATION OF TEST METHODS

8.1 All analytical test methods used in qualification, validation or cleaning exercises should be validated with an appropriate detection and quantification limit, where necessary, as described in Chapter 6 of the EU-GMP guide Part I.

8.2 Where microbial testing of product is carried out, the method should be validated to confirm that the test product does not influence the result.

8.3 Where microbial testing of surfaces in clean rooms is carried out, validation should be performed on the test method to confirm that sanitising agents do not influence the result.

9. CLEANING VALIDATION

9.1 Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Where different equipment is grouped together a justification of the specific equipment selected for cleaning validation is expected.

9.2 A visual check for cleanliness may form an important part of the acceptance criteria for cleaning validation however, it is not acceptable for this criterion alone to be used. Repeated cleaning “until clean” is also not considered an acceptable approach.

9.3 It is recognised that a cleaning validation programme may take some time to complete and validation with ongoing verification after each batch may be required. The level of data from the verification to support a conclusion that the equipment is clean should be evaluated.

9.4 Validation should consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities should be validated. Where a manual process is used, an assessment should be performed to determine the variable factors which influence cleaning effectiveness, e.g. operators, the level of detail in procedures such as rinsing times etc. For manual cleaning, if variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.

9.5 Limits for the carry over of product residues should be based on a toxicological evaluation to determine the product specific permitted daily exposure (PDE) value. The justification for the selected PDE value should be documented in a risk assessment which includes all the supporting references. The removal of any cleaning agents used should also be confirmed.

Acceptance criteria should consider the potential cumulative effect of multiple equipment in the process equipment train.

9.6 The potential for microbial and, or if relevant, endotoxin contamination, should be assessed during validation. The influence of the storage time before cleaning and the time

between cleaning and use taken into account to define (dirty and clean) hold times for the cleaning validation.

9.7 Where campaign manufacture is carried out, the impact on the ease of cleaning between batches should be considered and the maximum length of a campaign (in both time and number of batches) should be the basis for cleaning validation exercises.

9.8 Where a worst case product approach is used as a cleaning validation model, the rationale for selection of the worst case product should be justified and the impact of new products to the site assessed. When there is no single worst case product when using multi-purpose equipment, the choice of worst cases should consider toxicity and PDE value as well as solubility. Worst case cleaning validation should be performed for each cleaning method used.

9.9 Cleaning validation protocols should detail the locations to be sampled, the rationale for the selection of these locations and define the acceptance criteria.

9.10 Sampling should be carried out by swabbing and/or rinsing at the last stage of cleaning or by other means depending on the sampling location. The swab material should not influence the result. If rinse methods are used, the sampling should be performed during the final rinse in the cleaning procedure. Recovery should be shown to be possible from all materials used in the equipment with all the sampling methods used.

9.11 Typically the cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated.

9.12 For investigational medicinal products or products which are only manufactured infrequently, cleaning verification may be used instead of cleaning validation. If used, cleaning verification after each batch should be based on the principles in this section of the Annex,

9.13 Where cleaning validation has shown to be ineffective or is not appropriate for some equipment, dedicated equipment should be used for each product.

10. RE-QUALIFICATION

10.1 Facilities, utilities, systems, equipment should be evaluated at an appropriate frequency to confirm that they remain in a state of control.

10.2 Where additionally re- qualification is necessary and performed at a specific time period, the period should be justified and, the criteria for evaluation defined. Furthermore the possibility of incremental changes should be assessed.

10.3 Where manual processes are used, such as for cleaning of equipment, the continued effectiveness of the process should be confirmed at a justified frequency.

11. CHANGE CONTROL

11.1 The change process is an important part of knowledge management and should be handled within the pharmaceutical quality system.

11.2 Written procedures should be in place to describe the actions to be taken if a planned change is proposed to a starting material, product component, process,

equipment, premises, product range, method of production or testing, batch size, design space or any other change during the lifecycle that may affect product quality or reproducibility.

11.3 Where design space is used, the impact on changes to the design space should be considered against the registered design space within the Marketing Authorisation and the need for any regulatory actions assessed.

11.4 Quality risk management should be used to evaluate planned changes to determine the potential impact on product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance and on any other system to avoid unintended consequences and to plan for any necessary process verification or requalification efforts.

11.5 Changes should be authorised and approved by the responsible persons or relevant functional personnel in accordance with the pharmaceutical quality system.

11.6 Supporting data should be generated to confirm that the impact of the change has been demonstrated prior to approval.

11.7 Following implementation, and where appropriate, an evaluation of the effectiveness of change should be carried out to confirm that the change has been successful.

GLOSSARY

Definitions of terms relating to qualification and validation which are not given in other sections of the current EU Guide to GMP are given below.

Bracketing approach:

A validation scheme/protocol designed such that only batches on the extremes of certain predetermined and justified design factors, e.g., strength, batch size, pack size are tested during process validation. This approach assumes that validation of any intermediate levels is represented by the extremes validated. Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Change Control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action to ensure and document that the system is maintained in a validated state.

Cleaning Validation

Cleaning validation is documented evidence that an approved cleaning procedure will remove all traces of the previous product used in the equipment.

Concurrent Validation

Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches.

Continuous process verification

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)

Control Strategy:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Critical process parameter (CPP)

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)

Critical quality attribute (CQA)

A physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired product quality. (ICH Q8)

Design qualification (DQ)

The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

Design Space

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8)

Installation Qualification (IQ)

The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer’s recommendations.

Knowledge management

A systematic approach to acquire, analyse, store and disseminate information

Lifecycle

All phases in the life of a product, equipment or facility from initial development or use through to discontinuation of use.

Ongoing Process Verification (also known as continued process verification)

Documented evidence that the process remains in a state of control during commercial manufacture.

Operational Qualification (OQ)

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

Performance Qualification (PQ)

The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

Process Validation

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Product realisation

Achievement of a product with the quality attributes to meet the needs of patients, health care professionals and regulatory authorities and internal customer requirements. (ICH Q10)

Prospective Validation

Validation carried out before routine production of products intended for sale.

Quality by design

A systematic approach that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management.

Quality risk management

A systematic process for the assessment, control, communication and review of risks to quality across the lifecycle. (ICH Q9)

Simulated Product

A material that closely approximates the physical and, where practical, the chemical characteristics (e.g. viscosity, particle size, pH etc.) of the product under validation. In many cases, these characteristics may be satisfied by a placebo product batch.

State of control

A condition in which the set of controls consistently provides assurance of continued process performance and product quality.

Traditional approach

A product development approach where set points and operating ranges for process parameters are defined to ensure reproducibility.

Worst Case

A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.