PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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RECOMMENDATIONS

ON

QUALIFICATION AND VALIDATION

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TABLE OF CONTENTS

1. DOCUMENT HISTORY

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2. INTRODUCTION

The basic principles and application of qualification and validation are described in Annex 15 to the PIC/S and EU Guide to GMP.

This document updates and renames the previous document, PI 006-3 dated 25 September 2007 titled 'Recommendations on validation master plan, installation and operational qualification, non-sterile process validation, cleaning validation' following the revision of Annex 15 in 2015. It comprises individual recommendations on various topics of interest relating to qualification and validation in pharmaceutical manufacturing establishments.

2.1 Purpose of the Document

2.1.1 The topics in this document reflect some of the areas in pharmaceutical manufacture identified by PIC/S Inspectorates which require additional guidance from that given in the PIC/S GMP Guide Annex 15.

2.1.2 The purpose of this document is therefore to provide guidance and a training resource for GMP inspectors and the pharmaceutical industry that promotes medicinal quality assurance through a GMP compliant validation program.

2.2 Scope of the Document

2.2.1 The principles defined in the individual sections in this document equally apply to the manufacture of active pharmaceutical ingredients (APIs), intermediates as well as finished dosage forms.

2.2.2 At the time of issue, this document reflected the current expectations in these areas. It is not intended to be a barrier to technical innovation or the pursuit of excellence.

2.2.3 It should be noted that this document does not cover the validation of computer systems which impact GMP which is covered in the PIC/S GMP Guide Annex 11 and does not cover the validation of analytical test methods (6.4), in depth, as there is already detailed published guidance on this topic. It also does not include validation topics already included in other specialised PIC/S documents (e.g. PIC/S PI 007 *Recommendation on the Validation of Aseptic Processes*). However, the principles which apply to these areas are generally reflected in this document as well.

2.3 Aims of Qualification and Validation

2.3.1 The aim of qualification studies is to provide documentary evidence that facilities, supporting utilities, equipment and systems are suitable for their intended use.

2.3.2 The validation programme aims to demonstrate that control strategies are robust and that manufacturing processes are reproducible to ensure that any potential sources of variability are minimised.

2.4 Terminology

2.4.1 In this document, the term ‘qualification’ refers to facility, supporting utilities, equipment, and systems qualification. Validation in this document refers to process validation, cleaning validation, and method validation.

2.5 General Comments on Qualification and Validation

2.5.1 Any new, or where there are changes to existing facilities, supporting utilities, equipment and systems which may directly or indirectly affect the quality of the medicinal product, should be qualified.

2.5.2 Qualification and validation are an established requirement of a pharmaceutical quality system. It is important that a manufacturer has an appropriate understanding and control of all systems and processes that may directly or indirectly impact medicinal product quality. Approaches to qualification and validation should be continually reassessed and updated to incorporate modern concepts. (e.g. improvements in product development processes, technological advances and greater use of statistical tools).

2.5.3 Appropriate documentation of qualification and validation work is important to ensure the work performed can be clearly understood and complies with GMP.

2.5.4 It is a GMP requirement to identify what qualification and validation work is necessary to provide evidence of adequate control. Detailed understanding of pharmaceutical processing and knowledge of the product supported by scientific data are important to help determine what aspects of an operation are considered critical.

2.5.5 Qualification and validation may be addressed by a manufacturer in a variety of acceptable ways and different approaches will be considered by the inspector so long as they comply with GMP principles.

2.5.6 The expertise of suppliers, contractors and consultants may be utilised for qualification and validation work. In such cases, the responsibility lies with the contract giver to ensure that the required quality standards for the work are met.

2.5.7 Qualification and validation activities should be conducted using a lifecycle approach. The methodology, approach and documentation applied should be appropriate to the lifecycle stage of the facility, supporting utilities, equipment systems, or processes.

2.5.8 Data governance should be considered in all aspects of qualification and validation. All members of a project should understand their role in ensuring the integrity of data.

2.5.9 Where acceptance criteria for qualification and validation are not met, the deviation system should be used as directed in governing documents (e.g. the Validation Master Plan (VMP), validation protocol, etc.). See 3.4.3 (l)

2.6 Change Control (Note: For the purpose of this document, change control and change management are considered equivalent), see also PIC/S PI 054 *Recommendation How to Evaluate and Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management)*)

2.6.1 A robust change control process within the manufacturer's pharmaceutical quality system is important in maintaining the qualification and validation status of facilities, supporting utilities, equipment, systems, and manufacturing processes. Change control is often the starting point for qualification and validation work.

2.6.2 The commitment to change control should be re-emphasised in all high-level documents in the organisation such as the Quality Manual and the VMP.

2.6.3 Quality risk management principles should be used to evaluate changes to determine their potential impact on product quality, pharmaceutical quality systems, documentation, qualification and validation status, regulatory status, calibration, maintenance, and any other system to avoid unintended consequences and to plan for the necessary qualification and validation efforts.

2.6.4 Complex projects may be initiated from one principal change control but then branch out into various child change controls or be incorporated into a project management system or plan to reduce complexity and ensure control.

2.6.5 Changes should be approved at an appropriate level in the organisation. For complex changes, a change control board, or similar group, may be formed to ensure that all significant changes are given the appropriate attention, oversight, and inputs from appropriate disciplines to increase the chances of a successful outcome. The change control board (or equivalent) should consist of appropriately qualified personnel from all impacted departments.

2.6.6 Change controls normally require individual approval by different departments at different stages in the process such as:

a) approval to proceed with the change,
b) approval of the completed change actions, and
c) approval of effectiveness checks where required.

The Quality Unit should be involved in the approval of all change controls.

2.6.7 All actions resulting from a change control should have assigned timelines which are tracked to completion to ensure a state of control. Timelines may be extended, if permitted in the change control procedure, with appropriate authorisation and considering quality risk management principles. Multiple

extensions and failures to meet timelines may be indicative of a lack of control or inadequate resources.

2.6.8 Where appropriate, the effectiveness of a change should be evaluated after implementation. The effectiveness check should define quantifiable measures where possible (e.g. for a complaint of a missing leaflet in a product, a change control to strengthen the in-process controls as well as process robustness could be assessed for its effectiveness by reviewing 6 months of post change data relating to the performance of the process and new complaints). Where an effectiveness check is not required, a justification for not performing one should be documented.

2.6.9 All changes should be tracked in a manner which allows data gathering and trend identification for individual products, departments, production lines, etc. Tracking can also be used to develop quality management performance metrics to ensure that the allocated timelines are achieved, and the necessary resources can be allocated, or reallocated as required to achieve and maintain a state of control.

2.7 Organisation, Planning and Responsibilities for Qualification and Validation

2.7.1 A multidisciplinary approach to qualification and validation in pharmaceutical manufacture is usually required involving internal departments such as Production, Quality Unit, Engineering, Research and Development as well as external contractors or equipment suppliers.

2.7.2 Management must ensure that the manufacturer has the appropriate expertise and knowledge to conduct qualification and validation studies. This is especially important due to the increasing complexity of some validation studies for advanced technologies. Such projects may require the involvement of expertise across the organisation and, if necessary, from outside the organisation.

2.7.3 Irrespective of whether qualification and validation are performed by internal or external resources, there should be appropriate quality oversight over the whole qualification and validation programme. The manufacturer's responsibilities extend to ensuring regulatory compliance, to perform any necessary notifications to regulatory agencies and to comply with any post-marketing commitments related to qualification and validation where applicable.

2.7.4 It is the responsibility of the manufacturer to fully document the activities associated with the qualification and validation programme and to assure review by all appropriate internal departments.

2.7.5 It is the responsibility of the manufacturer to define the respective responsibilities of its personnel and of external contractors in the qualification and validation programme. All activities should be fully documented and reviewed by appropriate personnel.

2.7.6 It is imperative that the most senior level of management within the organisation understand the personnel, time and financial resources required to execute a

qualification and validation programme and commits the necessary resources to the work.

2.8 Quality Risk Management (QRM) Principles in Qualification and Validation

2.8.1 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 qualification and validation should be based on a justified and documented risk assessment of the facilities, supporting utilities, equipment, systems, and processes.

2.8.2 Risk assessment are used to ensure that qualification and validation work focuses on areas most likely to impact product quality and patient health.

2.8.3 Risk assessments may have different objectives depending on the qualification or validation work performed.

2.8.4 The risks associated with qualification and validation work are numerous and specific to the work to be performed. Risks will vary depending on the technology used, complexity of the manufacturing process, experience of the site personnel, knowledge of specific dosage forms and level of subject matter expert (SME) support.

2.8.5 After assessment (i.e. hazard identification, risk analysis and evaluation) of any qualification and validation lifecycle risks, a decision should be made on the appropriateness of the control strategy to accept risks or further reduce risks.

2.8.6 Other supplementary risks during qualification and validation may also need to be considered during planning such as:

Risk to adjacent operations – The risk to adjacent or connected facilities should be considered when performing qualification or validation work.

Risk to shared facilities and equipment – The risk of cross-contamination when using shared equipment, shared utilities, and/or common HVAC systems should be considered when performing qualification or validation work.

Supply chain risk – The risk of supply chain shortages or delayed product launches should be considered during planning phases of qualification and validation with contingencies considered.

3. VALIDATION MASTER PLAN (VMP)

3.1. Principle

3.1.1 Qualification and validation activities are complex and require careful and detailed planning and experienced personnel to be successful. The VMP should be risk-based, scientifically sound and define the manufacturer's overall approach to qualification and validation. The VMP therefore serves as the template from which all qualification and validation activities are developed. It ensures that all qualification and validation activities proceed in a structured

manner according to formally authorised standard operating procedures (SOPs).

3.2 Purpose

3.2.1 The VMP should present an overview of the entire qualification and validation operation, its organisational structure, its content, and planning. One of the key components of the VMP is the list or inventory of facilities, supporting utilities, equipment, systems, and processes which require qualification and validation. A schedule should be included for the completion of this work and for lifecycle review of the state of control of previously qualified/validated systems and processes.

3.2.2 A VMP helps all individual members of the validation team to understand their tasks and responsibilities.

3.2.3 A VMP helps GMP inspectors to understand the manufacturer's approach to qualification and validation, the organisation set-up for these activities, and to what extent qualification / validation projects are planned and managed.

3.3 Scope

3.3.1 All qualification and validation activities impacting on medicinal products and related GMP controls within the organisation should be included in a VMP.

3.3.2 It should include all qualifications, re-qualifications, prospective and concurrent process validations as well as ongoing (or continued) process verification and revalidation activities.

3.3.3 A VMP establishes the overall qualification and validation strategy within an organisation. A VMP could also be used in specific situations (e.g. for large projects such as the construction of a new facility where a master planning approach is required to ensure coordination, control and execution of individual qualification and validation activities within the larger project). In this situation, it is used to ensure completion of all activities rather than changing the qualification and validation strategy already established in the VMP.

3.4 Format and Content

3.4.1 The VMP should be a summary document and therefore be brief, concise, and clear. It should not repeat information documented elsewhere but should include, as a minimum, the information indicated below, or refer to existing documents such as policy documents, SOPs, validation protocols and reports.

3.4.2 The VMP should be approved by management and regularly reviewed, and updated as necessary, following any changes to facilities, supporting utilities, equipment, systems, and processes.

3.4.3 A VMP should contain information on the following topics:

a) **Introduction**

The manufacturer's validation approach, general description of the scope of operations covered by the VMP, location and schedule (including priorities).

b) **Organisational structure for all qualification and validation activities**

Personnel responsibility for:

i. the VMP;
ii. protocols for individual validation projects;
iii. qualification and validation work;
iv. reports and document preparation and control;
v. approval, authorisation of qualification and validation protocols and reports in all stages of the process;
vi. the tracking system for documents; and
vii. training needs to support qualification and validation.

c) **Use of a Worst-case Approach**

A common approach in qualification and validation studies is to challenge processes, systems, etc. The rationale behind any challenge and or "worst case" situation should be explained. Consideration should be given to the grouping of products / processes to validate "worst case" situations. Where "worst case" situations cannot be simulated, the rationale for the groupings made should be defined. All considerations should be based on quality risk management principles. "Worst case" should not be used to validate to the edge of failure but to ensure sufficient robustness to accommodate the boundaries of process variation.

d) **Plant / Process / Product Description**

Provides a cross reference to other documents. A rationale for the inclusion or exclusion of qualification and validation, the validation approach used on site and the extent of validation should be included.

e) **Specific Process Considerations**

Includes specific characteristics or requirements of the plant, process, etc. that are critical for yielding a quality product and need extra attention.

f) **List of Products / Processes / Systems to be Qualified / Validated**

All qualification and validation activities in the VMP should be summarised and compiled to address:

i. all facilities, supporting utilities, equipment, systems, and processes that are subject to qualification and validation with a description of the extent of qualification and validation required;
ii. the validation type used (i.e. prospective or concurrent). If concurrent validation is used, the products using this should be listed;

iii. justification for the frequency of re-qualification and system in place for ongoing process verification should be listed; and
iv. current status and future planning.

g) **Documentation Format**

The template document format to be used for any qualification and validation protocols and reports should be defined.

h) **Required SOPs**

A list of all relevant SOPs for qualification and validation should be included.

i) **Acceptance Criteria**

Guidance should be given on developing acceptance criteria.

j) **Planning & Scheduling**

Staffing requirements (including training needs), ancillary testing equipment and any other specific requirements to complete the qualification and validation activities should be considered during planning but do not necessarily need to be included in the VMP. The frequency of update of the VMP should be defined.

k) **Change Control**

A statement of the manufacturer's commitment to controlling changes to facilities, supporting utilities, equipment, processes, and systems which may directly or indirectly affect the quality of the medicinal product.

l) **Deviation Management**

A description of how the manufacturer will manage deviations during qualification and validation work should be defined (note, in addition to instances when the protocol was not executed as specified, deviations also include results which fail to meet the pre-defined acceptance criteria. Any implications for the qualification/validation should be discussed in the report). In addition to recording deviations in the qualification or validation report, it is important that deviations are also visible within the manufacturer's deviation system to aid investigations if further deviations occur during routine production.

m) **Data Integrity**

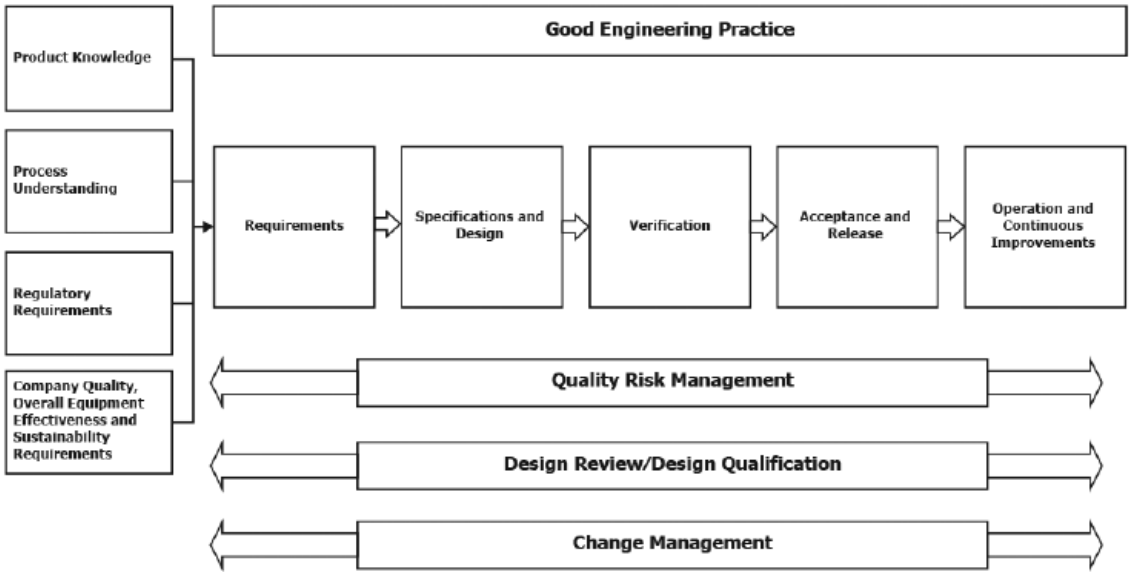
Requirements to confirm data integrity in qualification and validation reports should be defined. This confirmation should be completed independently by personnel who are not executing the qualification and validation work as a formal protocol depending on the nature of the work performed.

4. PREQUALIFICATION AND QUALIFICATION STAGES FOR FACILITIES, SUPPORTING UTILITIES, EQUIPMENT AND SYSTEMS

4.1 Principle

4.1.1 This section considers the qualification approach which has been long established and proven to work in practice. However, there are different approaches to qualification that use different terminology than those presented in this guide which are based on good scientific or engineering practices (e.g. ASTM E2500) which could also be applicable in appropriate circumstances. Irrespective of the approach used, the intent is to show that facilities, supporting utilities, equipment or systems perform as expected and are fit for purpose.

Figure 1: ASTM E2500-25 The Specification, Design, and Verification Process[1]



4.1.2 The qualification process is conducted to demonstrate that facilities, supporting utilities, equipment, or systems are suitable for their intended function. These studies should demonstrate appropriate installation and operation, and that all necessary procedures have been established to ensure fitness for use and state of control. This is accomplished through a combination of verifying that appropriate documentation and records are available and by conducting tests to verify that the equipment is functioning as intended.

4.1.3 These recommendations are intended to cover both the installation and operation of new or modified facilities, supporting utilities, equipment, or systems.

[1] Used with permission of ASTM International from ASTM E2500-25, Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment Science and Risk Based Approach; permission conveyed through Copyright Clearance Center, Inc.; www.astm.org.

4.1.4 The basic principles are as follows:

a) Requirements should be established during the preparation of the User Requirements Specifications (URS).

b) Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) studies should be linked to the URS and Design Qualification (DQ) and verify that facilities, supporting utilities, equipment, or systems meet the established requirements. This essentially verifies that they are fit for their intended purpose.

c) A formal release of the equipment, utility or system to the next stage in the qualification process should be authorised. Conditional approval to proceed to the next qualification 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.

d) The IQ study should verify that the facility, supporting utility, equipment or system have been correctly installed according to design and construction specifications and/or equipment manufacturer recommendations.

e) The OQ study should verify that the functional requirements established in the original engineering design and specifications (URS and DQ) for the facilities, supporting utilities, equipment, or systems are met. The study should establish the range of parameters under which the facility, supporting utility, equipment, or system will perform as intended throughout the anticipated operating ranges.

f) The PQ should verify that the facility, supporting utility, equipment or system operate as designed and required by the user using actual production material, qualified substitutes or simulated product that have been proven to show equivalent behaviour under normal operating conditions.

g) Qualification studies should also demonstrate that the manufacturer has implemented appropriate procedures to ensure that the facility, supporting utility, equipment, or system will continue to operate in a state of control. This includes verifying that appropriate operation, maintenance, calibration, and cleaning procedures and requirements have been developed and that employees have been appropriately trained. Procedures for the above will normally be in draft form at the start of the qualification effort and finalised/approved as part of the manufacturer's SOP program prior to the completion of the qualification study.

4.1.5 The basic principles outlined above apply to all qualification studies. The actual nature and scope of the qualification effort should, however, be based on the complexity and criticality of the facility, supporting utility, equipment, or system being qualified. For example, the level of qualification effort required for an autoclave would likely be greater than the qualification effort required for a packaging leaflet insertion machine.

4.1.6 Protocols, procedures, specifications, and acceptance criteria for test results should be reviewed, checked, and authorised where required in the qualification exercise. It is expected that all relevant personnel and the Quality Unit, will approve these documents.

4.1.7 The manufacturer may conduct a pre-delivery check at the supplier site for some systems (Factory Acceptance Testing – FAT) or conduct testing once the equipment has arrived at the pharmaceutical site (Site Acceptance Testing – SAT). FAT and SAT testing may be used with appropriate justification to reduce the required scope of IQ and OQ testing.

4.1.8 Deviations may be identified during prequalification and qualification activities. These deviations should be appropriately managed and understood, with appropriate CAPA raised, prior to the facility, supporting utility, equipment and systems being considered fit for purpose.

4.2 Prequalification Stages

As indicated above, a change control is a common starting point for all qualification and validation activities for most projects which would be expected to include an element of quality risk management to identify and mitigate any potential risks. This section examines prequalification stages such as the URS, DQ and confirmation aspects such as FAT and SAT.

4.2.1 User Requirements Specification (URS)

The URS defines the customer requirements and expectations for the facility, supporting utility, equipment, or system to be purchased or built in-house. The URS should be developed with input from different departments such as production, engineering, quality, technical services, or others where appropriate. The quality of the inputs at this stage will increase the chances of selection of the correct provider and a successful project. It is also useful to detail which elements of the specification are essential, or flexible so that the pool of potential suppliers is unnecessarily limited. Any GMP risks identified during the development of the URS should be appropriately assessed by risk assessment as for all qualification stages.

The URS should be a controlled document with subsequent versions updated through the document change control system as the selection process moves forward and understanding of the facility, supporting utility, equipment, or system increases.

4.2.2 Design Qualification (DQ)/Design Specification (DS)

This is the stage where the user requirements specifications are reflected in the design, taking into account the process and product requirements, quality and regulatory requirements the critical aspects necessary for implementing the requirements and risk controls. Risk analysis is often part of this phase so that any risks identified can be controlled via design changes. Manufacturers often perform this activity by going through the GMP guidance to compare against the requirements listed in their URS.

In some cases, the manufacturer may decide to prepare a separate DS which explains how the design meets the requirements in the URS. The DS may include the user requirement specifications, drawings, materials of construction, spare parts lists, expected output, capacity, functions, and vendor details.

The DQ verifies that the facility, supporting utility, equipment, or system chosen meet the requirements of the URS and DS and is a documentation verification process.

4.2.3 Factory Acceptance Testing (FAT)

FAT provides an opportunity for the manufacturer to review the equipment to be purchased, and confirm that it meets the requirements in the URS at the vendor prior to delivery. It can also be used to identify any missing requirements or faults and ensure that these are rectified before delivery to the site. It also provides the opportunity to review documentation such as materials of construction, engineering, electrical and pneumatic drawing to identify any missing documents which saves time and explanation as they should be readily available at the manufacturer. In addition to documentation review, some IQ/OQ tests may be able to be performed at FAT so long as there is a justification that any tests will not be affected by shipment to the site.

FAT is also a useful opportunity for initial training of key personnel who will be involved in future operation, maintenance and validation of the equipment, supporting utility, or system. It is important to ensure that any materials required for test runs are sent to the manufacturer in advance of the FAT and that quantities are sent which allow meaningful machine trials. Where appropriate, substitute products should be considered for trial runs rather than active ingredients as there may be inadequate health and safety controls at the supplier. There should be a FAT protocol and report which are both formally approved.

4.2.4 Site Acceptance Testing (SAT)

Similarly, SAT provides an opportunity for the manufacturer/supplier to confirm that the equipment will perform in accordance with the URS when installed at the manufacturing site. It is an opportunity for personnel to obtain greater understanding and knowledge and to confirm that any alterations made at the FAT have been completed. There should be an SAT protocol and report which are both formally approved.

4.3 Qualification Stages

4.3.1 Installation Qualification (IQ)

4.3.1.1 The IQ is designed to ensure that the facility, supporting utility, equipment, or system is correctly installed. It should be executed by appropriately qualified site personnel or by a contracted and appropriately qualified third party.

4.3.1.2 The IQ should be executed against an approved protocol that has been developed and finalised. Protocols will confirm that equipment specifications,

plant functional specifications and piping & instrumentation diagrams (P&IDs) are correct. Any changes to the original design criteria should be documented with an explanation to support the change, and appropriate modifications made to equipment specifications, plant functional specifications and P&IDs if required.

4.3.1.3 Calibration requirements are identified at this stage and a list of components that require calibration and the appropriate calibration ranges listed.

4.3.1.4 It is also important that the type and nature of procedures and other controls to allow use of the equipment in a controlled manner are evaluated prior to starting the qualification study. Draft procedures written at this stage would normally include set-up, operation, maintenance, calibration, and cleaning requirements which can be finalised once personnel gain further knowledge and experience with the equipment. Other procedures may be required based on the nature of the equipment or system under evaluation. For example, computerised systems may require access control procedures and procedures outlining regular data and audit trail checks to be completed.

4.3.1.5 IQ should include, but is not limited, to the following:

a) verification that approved engineering drawings, P&IDs and specifications are available and current;
b) verification that components, instrumentation, equipment, pipe work and services/utilities have been properly installed in a manner that complies with all engineering documentation and with all specifications developed during the project planning stage;
c) verification that proper supplier records and documentation are available for all equipment, systems, and components — this includes supplier drawings as well as any supplier manuals for the proper maintenance, operation, and cleaning of the equipment;
d) assurance that all materials of construction meet the requirements detailed in the URS;
e) verification that all components requiring calibration have been calibrated as appropriate; and
f) assurance that required procedures are available to ensure that equipment and/or systems can be operated in a controlled manner — such procedures may still be in draft form at the IQ study as they may require further modification based on the results of the operational and/or PQ stages.

4.3.2 Operational Qualification (OQ)

4.3.2.1 OQ evaluates that the facility, supporting utility, equipment, or system operates in the expected manner. OQ is a key component of the qualification process and is often performed by appropriately qualified site personnel or by contracted and appropriately qualified third parties.

4.3.2.2 OQ includes evaluation of the critical variables (parameters) required for the effective operation of the facility, supporting utility, equipment, or system and establishes the appropriate parameter ranges based on risk assessment principles. The results should be confirmed against pre-established acceptance criteria to demonstrate that the facility, supporting utility, equipment, or system meets the requirements in the URS and DQ.

4.3.2.3 All testing equipment should be identified and calibrated before use. Test methods should be validated and authorised, and the resulting data collected, evaluated, and approved before incorporation into the final OQ report.

4.3.2.4 Testing during the OQ stage should be conducted using the SOP intended for the facility, supporting utility, equipment, or system. The procedures may still be in draft form but should be finalised before the final approval of the OQ report.

4.3.2.5 The OQ should be executed against an approved protocol that has been developed and finalised. The plans for the OQ should identify the studies to be undertaken on the critical variables and the sequence of those studies, the measuring equipment to be used and the acceptance criteria to be met. Studies on the critical variables should incorporate specific details and tests that have been developed from specialist knowledge of the process and how the facility, supporting utility, equipment, or system will work as defined in the design and equipment specification.

4.3.2.6 The completion of a successful OQ should allow the finalisation of operating procedures for the facility, supporting utility, equipment, or system which should be used as the basis for operator training.

4.3.2.7 The completion of satisfactory IQ and OQ should permit use of the equipment/plant and supporting utilities/facilities/systems for PQ. (See 4.3.3.2)

4.3.3 Performance Qualification (PQ)

4.3.3.1 PQ verifies that the facility, supporting utility, equipment, or system operates in the expected manner using actual or appropriate simulated production materials under normal operating conditions and is performed by appropriately qualified site personnel or by contracted and appropriately qualified third parties.

4.3.3.2 PQ will normally be conducted following the successful completion of the IQ and OQ. It may, in some cases, be appropriate to perform in conjunction with the OQ or as part of process validation. The PQ should be executed against an approved protocol that has been developed and finalised.

4.3.3.3 The PQ should be conducted over an appropriate time period to cover all activities occurring during normal operating conditions (e.g. adjustments, stoppages, personnel changes, material replenishment, door opening of refrigerators, seasonal variations). The rationale for the time period and test conditions to be evaluated during the PQ should be formally documented.

4.3.3.4 It is expected that additional samples over and above those normally used for in process quality control (IPQC) checks are taken (e.g. taking additional samples only at the beginning, middle and end of the batch would not be appropriate). If the IPQC checks are performed every hour, then a 15-minute sampling plan may be required, and potentially additional tests may be required (e.g. uniformity tests, particle size).

4.3.3.5 Statistical tools may be used in PQ with process control charts. While simple data trend charts may be useful, other tools such as process capability index (Cpk), process performance index (Ppk) or multivariate statistical process control (MSPC) may be more powerful.

4.4 Re-Qualification

4.4.1 Any modifications to facilities, supporting utilities, equipment and systems should be assessed, documented, and approved within the change control system. 'Like for like' changes could be handled within the planned preventative maintenance system, so long as the 'like for like' decision is documented, justified, and is approved by the Quality Unit.

4.4.2 Manufacturers should review facilities, supporting utilities, equipment, and systems at predetermined intervals to ensure that they remain within a qualified state of control. This could include a review of all equipment changes, maintenance records as well as other quality system information or trending available for the equipment (e.g. associated deviations). The review process may determine that additional qualification studies are required as a series of minor changes may represent a major change over time.

4.4.3 The frequency of the review process should be justified based on quality risk management principles including equipment criticality.

4.4.4 Although the Product Quality Review is product related, a statement could be added as to whether, based on the evidence collected in the PQR, the equipment appears to be functioning in the expected manner.

5. PROCESS VALIDATION

5.1 Principles

5.1.1 Process Validation is the means of providing documentary evidence that processes (within their specified design parameters) are capable of repeatedly and reliably producing a product of the required quality. The process validation programme should confirm that process establishes and maintains a **state of control**.

5.1.2 Improvements in the product development process, advances in technology and greater use of statistical tools have changed the approach taken for process validation as outlined below.

5.1.3 These recommendations are applicable to the manufacture and packaging of pharmaceutical dosage forms, however, have not been tailored to specific product types (e.g. sterile, biotechnology or radiopharmaceutical products) as well as active pharmaceutical ingredients and intermediates.

5.1.4 These recommendations may be applied to the manufacture of investigational medicinal products (IMPs) as required in the specific GMP requirements for the product.

5.1.5 These recommendations cover the initial validation of new processes, ongoing process verification during commercialisation, and revalidation of processes, which after launch, are modified and/or transferred to other manufacturing sites.

5.2 General

5.2.1 Manufacturing processes may be developed using a traditional or an enhanced (Quality-by-Design) approach, as defined in the International Council for Harmonisation (ICH) Q8 Pharmaceutical Development, or a hybrid of the two. Irrespective of the approach used, manufacturers should have confidence that processes are adequately designed, understood and controlled prior to starting a process validation study.

5.2.2 The development of the process design and the associated routine control strategy, including any adjustments made during scale-up and technology transfer of the process to the production site, should be considered as an integral input to the process validation. If required, pre-validation, engineering or trial runs should be performed prior to formal process validation.

At the start of formal process validation, information from development studies or other sources (for instance, the manufacturing history of comparable processes) should be available at the manufacturing site[2]. For details see section 5.3.1 of this document.

If the manufacturing process involves a design space and/or a continuous process verification approach to validation is pursued, further additional information may be required; for details see section 5.5 of this document.

5.2.3 It would normally be expected that the initial commercial-scale process validation study is completed prior to the manufacture of product batches that are intended for sale (**prospective** validation see section 5.3). Batches manufactured according to a new or modified process should usually be released to the market only when both within-batch and between-batch variability of the manufacturing process have been demonstrated to meet pre-defined limits.

There are other types of process validation:

Concurrent validation (where execution of the validation protocol occurs simultaneously with the commercialisation of the process validation batches) could be used in exceptional circumstances, see section 5.4 below.

Retrospective validation is no longer considered an acceptable approach to process validation.

Legacy processes which had been validated according to previous standards should meet current process validation standards. This includes ongoing process verification (see section 5.6), including additional testing, if identified, through gap analysis and risk assessment.

[2] See ICH Q8 *Pharmaceutical Developmen*t Part II Section 1.

5.2.4 Normally batches manufactured for process validation should be the same size as the intended commercial scale batches. The smallest batch size might also need to be confirmed (e.g. where mixing equipment may need a minimum volume of material for effective operation).

5.2.5 Process validation should cover all marketed strengths of a product. **Bracketing** (e.g. full validation of the extremes such as the lowest and the highest strengths, while performing a reduced validation programme for intermediate variants) may be acceptable if the bracketing design is science-based and complies with quality risk management principles. Bracketed validation designs may need to be supplemented by additional testing during subsequent ongoing process verification (see section 5.6). A documented justification for a bracketing approach should be available.

5.2.6 The number of validation batch replicates should be based on sound science and the manufacturer's overall level of product and process understanding and demonstrable control. A risk assessment of the potential variability in the product is useful. Increased variability or risk should normally result in an increased number of batches and further intensification in sampling during the validation study to support the proposed commercial process and a basis for future sampling plans.

5.2.7 Challenge testing during process validation should be avoided as product development and any pre-validation/engineering/trial runs should have already defined the process parameters and identified any causes of variation. Challenge tests (only within the established parameters) might however be useful to close any remaining minor gaps arising from the risk assessment. There is also the possibility to perform additional testing during the subsequent ongoing process verification to address any issues so long as this is documented and justified.

5.2.8 Process validation is not a one time activity. Manufacturers are obliged to ensure that a manufacturing process remains in a state of control throughout the entire lifecycle of the product and process through monitoring that allows tracking of process performance over time to determine the need for any improvement or change. Unintended incremental changes of the process over time should be captured by ongoing process verification (see section 5.6). Intentional modifications of the process or site transfers should be assessed to determine if **revalidation** is required (see section 5.7).

5.2.9 It is acknowledged that it is not always possible to identify exactly the borderline between performance qualification (PQ) of a facility or equipment and validation of a manufacturing process. PQ and process validation together should ensure that the requirements of PIC/S GMP Annex 15 relating to both the qualification of facilities/equipment/utilities and the validation of processes are fully complied with, in a traceable manner. While PQ of equipment may be performed before process validation, the PQ may alternatively be incorporated into the Process Validation activities.

An appropriate means to avoid additional work is to consider the results of the PQ in the process validation risk assessment to determine the scope of the process validation (see section 5.3.2).

The main difference between PQ and process validation is their point of reference which in the case of PQ is the URS of the facility / equipment/utilities and in the case of process validation the Master Batch Record describing the process to be validated. If the equipment is purchased before the manufacturing process for which it is to be used is known or, where it is purchased for use in multiple products which are currently unknown, it is unlikely that a PQ can replace a process validation. Conversely if the equipment is purchased for a specific product using a defined process, a well-designed PQ could substitute for process validation assuming a detailed risk assessment was performed and determined risks have been managed to acceptable levels.

5.2.10 Routine quality control and process validation of finished products typically consist of testing random samples of the dosage form out of a population (batch). At initial commercial-scale process validation studies, larger sample sizes are critical to accurately characterize the variation throughout processing and the stability of the process. A significant body of data will support a robust analysis using appropriate and sophisticated statistical approaches. This uncertainty may be reduced using scientifically justified sampling designs and tools that enable enhanced detection and more precise quantification.

The application of such statistical tools requires significant expertise and the extent of their use should be dependent on the risk which data uncertainties may cause to patient health. Manufacturers should ensure that statistical designs and analyses, if applied, are used in a scientifically sound and correct manner (e.g. in compliance with respective ISO norms).

5.2.11 The application of statistical methods and acceptance criteria in validation should be considered for any parameter where the state of control of the process is of importance for patient health.

a) the statistical tools used may range from simple calculation of location and dispersion parameters (e.g. average and span or standard deviation) to more sophisticated ones, such as trend analyses or those applied in MSPC;
b) both intra- and inter-batch variabilities should be considered;
c) the sampling method (e.g. worst-case timepoints, locations, or stratified such as machine run time-related), the number of samples taken, the way of processing the obtained data and the acceptance criteria (e.g. a minimum Cpk) should be defined and justified in advance of the validation exercise;
d) for each selected parameter, the chosen statistical approach should allow for a science-based and clear statement on whether the process is in a state of statistical control; and
e) any statistical evaluation should involve both subject matter experts and statisticians.

5.3 Prospective Validation

5.3.1 Before commencing validation of a commercial manufacturing process, some **prerequisites** are required:

a) Description of the quality target product profile (QTPP) and related critical quality attributes (CQA) and critical process parameters (CPP);
b) the CQAs of the finished product, and if applicable of intermediate stages, should be known at the production site;
c) the CPPs, critical (starting or intermediate) material attributes (CMAs), and possibly other critical inputs (e.g. environmental conditions) should be known at the production site;
d) development, scale-up, technology transfer and any other reports containing process understanding should be available at the production site;
e) a full description of the process to be validated should be available, including the equipment and materials to be used, machine settings, and other relevant details;
f) the initial control strategy should be fully defined (stages at which tests are performed, type of tests, sampling schemes, acceptance criteria etc.);
g) all facilities, supporting utilities, equipment, or systems to be used for manufacture and control of the validation batches should be qualified;
h) all testing methods used during process validation should be validated;
i) all starting, packaging and all other materials to be used in the manufacturing process (e.g. supporting utilities, culture media, filters, single-use items) should meet pre-defined specifications and suppliers should have been qualified;
j) personnel performing the manufacture and testing of validation batches should be trained in their respective tasks;
k) a risk assessment of the process and its control strategy with the objective of determining scope, depth, and breadth of the process validation should have been performed (see section 5.3.2); and
l) based on the outcome of the risk assessment, an approved process validation protocol should be available which describes, in detail, the validation approach (see section 5.3.3).

5.3.2 The **risk assessment** of the manufacturing process and its control strategy should be performed in accordance with ICH Q9 Quality Risk Management principles.

Potential knowledge gaps (e.g. from incomplete development or scale-up of the process) should be adequately considered. The risk assessment should indicate the following:

a) criticality / non-criticality of quality attributes, process parameters, material attributes and other possibly relevant inputs such as environmental conditions;
b) the required scope of additional testing of CQAs, CPPs, CMAs and other elements that may impact quality;
c) any requirements to include validation batches into the ongoing stability programme;
d) the maximum allowable variance in acceptance criteria results for the additional controls;
e) number of validation batches required to simulate routine manufacturing conditions
f) aspects to be considered for market release of the validation batches (if planned);

g) aspects to be considered for a concurrent validation approach (if planned); and
h) aspects to be considered for a bracketing approach (if planned).

5.3.3 The process validation protocol should include all information itemised in section 5.22 of the PIC/S GMP Annex 15. The following additional information should also be provided:

a) a reference to the risk assessment on which the validation design is based;
b) a traceability matrix visualising how the outcome of the risk assessment is utilised for the validation protocol is also helpful;
c) the number of consecutive validation batches to be performed, including a justification for the number selected;
d) a description of how simulation of the varying routine conditions during manufacture should be realised, including the performance of challenge tests, if required;
e) a description and justification of the bracketing approach (as applicable);
f) details of methods for recording and evaluating results, including statistical analysis;
g) a summary of other (non-critical) attributes and parameters, which will be investigated or monitored during the validation activity and the reason for their inclusion; and
h) a description of the specific procedure for release and certification of validation batches (if applicable).

5.3.4 Manufacture of the validation batches should be conducted under the same conditions considered typical for subsequent routine manufacture.

Production personnel should be closely involved in the execution of the validation batches to build up their knowledge for subsequent routine manufacturing. All designated controls normally expected for routine production should apply to the validation batches with any deviations from procedures and protocols recorded and assessed for impact on the integrity of the validation.

Planned variations in manufacturing conditions should be defined in advance as part of the validation protocol, based on consideration of the risk.

The following aspects should also be considered:

- use of different API lots and, as applicable, different lots of raw materials;
- use of single or multiple alternative equipment;
- variation of hold times for raw materials and intermediate;
- variation of environmental conditions (e.g. temperature, relative humidity); and
- manufacture during different work shifts, including night shifts, during shift change (e.g. processes that span two or more shifts), and production pauses (if applicable).

Whenever variations in the manufacturing conditions cannot be planned (e.g. because they are dependent upon ambient weather conditions), they should, however, be recorded and assessed in the validation report reflecting how broadly they cover the expected ranges in routine production.

5.3.5 Validation batches produced at the start of the commercial lifecycle should be documented comprehensively, in a manner that supports data integrity.

5.3.6 The following items should be included in the validation report for process performance qualification:

a) a brief description of the process and a reference to the Master Batch Record used;
b) a reference to the validation protocol used;
c) a statement on whether the validation was executed according to protocol or whether there were any deviations;
d) a list of the validation batches manufactured and tested including any batch that may have been aborted or rejected during the validation exercise;
e) a brief report of the production of the validation batches, with focus on any significant events which occurred and to what degree it was possible to simulate routine conditions;
f) a summary and assessment of all data collected, including a reference to the raw data, and a statement on whether the predefined acceptance criteria were met or not;
g) a science-based evaluation of each deviation for impact on the overall outcome of the validation;
h) an overall evaluation of the validation results including justification for acceptance or rejection;
i) a statement on whether the process is robust and a decision to release or reject the process for commercial use;
j) a statement on whether the release of manufactured validation batches for commercial sale is intended; and
k) any recommendations to ensure the validated status of the process (e.g. the design of the ongoing process verification and/or the ongoing stability programme).

5.4 Concurrent Validation

5.4.1 Concurrent validation is the execution of the validation protocol concurrently with commercialisation of the validation batches. It does not negate the need for prospective validation to be performed. It is performed only in exceptional circumstances where there is a significant benefit to the patient, compared to the risk of not fully completing the validation. The risk mainly arises from releasing batches prior to understanding the inter-batch variability of the process (while typically intra-batch related data is and should be available at the time of batch release).

5.4.2 The decision to perform a concurrent validation must be taken in advance of the work and documented in the VMP and the specific validation protocol.

5.4.3 The intention to release batches prior to completion of the validation study must be justified, documented in the VMP for visibility and approved by authorised personnel. The justification should demonstrate that the advantage for the patient (e.g. ensuring product supply, no availability of similar products, etc.) significantly outweighs the risks to the patient resulting from incomplete validation knowledge.

5.4.4 A justification for release of batches may be stronger, the greater the medical need and the higher the level of understanding and experience with the manufacturing process. Therefore, concurrent validation is more likely when:

a) the product is therapeutically essential and cannot be easily replaced;
b) the process validation is performed according to a continuous verification approach (as opposed to the traditional approach (see section 5.5);
c) knowledge from a similar previously validated product (e.g. a different strength of the same product) exists; and
d) changes to an existing process requiring revalidation, have a foreseeable limited impact on product quality (e.g. a different tablet shape).

5.4.5 Concurrent release of a validation batch should be performed only if enough data is available to support the conclusion that the batch is uniform and meets all defined acceptance criteria, including validation criteria for the tests performed, and intensified monitoring that provides further data to confirm within-batch variability. The Qualified Person, or equivalent person, performing the batch disposition should take all related data which has been generated into consideration.

5.4.6 Expectations expressed for prospective validation (see section 5.3) also apply to concurrent validation, where applicable.

5.5 Acceptable Approaches to Process Validation Studies to Support Initial Commercialization

5.5.1 A manufacturing process may be validated according to either a traditional approach, a continuous process verification (CPV) approach, or a hybrid of the two.

The CPV approach can be selected only if the development of the manufacturing process was conducted according to Quality-by-Design principles (the 'enhanced' development approach according to ICH Q8) and/or if a scientifically justified routine control strategy was derived from other sources, for instance the manufacturing history of a comparable process.

A CPV approach to validation may require prior approval by the competent authority for product market authorisation.

Expectations expressed in sections 5.2, 5.3 and 5.4, respectively, apply to all validation approaches, where feasible.

5.5.2 The purpose of the **traditional approach** to validation is to confirm that the commercial process performs in a reproducible manner.

The number of consecutive batches should be scientifically justified for initial validation of a new process[3]. The data generated should be extensive to evaluate whether control has been established throughout batch processing and provide baseline data to support initial statistical evaluations. The number of batches will also be driven by the risk assessment as indicated in 5.2.6 and based on existing product and process understanding. An understanding of intra- and inter-batch process variability at full scale prior to initial validation studies, in some cases, may support flexible approaches (e.g., fewer replicate batches). However, such approaches are not appropriate where there is less extensive data and a lesser understanding of variability.

Any resulting weaknesses of the validation data package should be compensated by additional testing during the subsequent ongoing process verification (see section 5.6), as indicated by the respective risk assessment.

5.5.3 In the case of CPV**,** process performance is monitored continually in real time during manufacturing by applying on-line, in-line or at-line controls and by multivariate analysis of the data. Data evaluations may be used to regulate the process or to make corrective interventions.

CPV may be applied for a pre-determined period or number of batches, or permanently throughout the lifecycle of the routine process. This should be determined in advance in the protocol and be based on scientific justification.

Compared to a traditional validation approach, CPV tends to create stronger evidence of the uniformity of a batch and as a result, early release of batches manufactured and validated this way is more easily facilitated.

5.5.4 The method of CPV should be compliant with the officially approved quality dossier of the product and should be defined in detail in the respective work instructions. The way in which CMAs of incoming materials and intermediates, CPPs, CQAs are controlled and the methods for processing and using the accumulated data for process control should be described. Typically, monitoring and data evaluation are facilitated using Process Analytical Technology (PAT) and MSPC. Where MSPC is applied, this should be done in accordance with related ISO documents (e.g. ISO 3534-2).

5.5.5 For the selection of the parameters to be monitored, it is essential to understand the functional relationships that link material attributes and process parameters to product CQAs (see ICH Q8).

Process understanding gained during the Quality-by-Design development work and possibly thereafter, and risk considerations should be used as a basis for the CPV method. Monitoring of critical parameters should be done at enough frequency so that any changes in the process or product quality are detected early.

[3] Note the recommendation in 5.5.2 for scientific justification of the number of consecutive batches builds upon the current PIC/S Annex 15 requirement that indicates it is generally considered acceptable that a minimum of three consecutive batches manufactured under routine conditions could constitute a validation of the process. The recommendation in 5.5.2 is intended to advance the application of science and QRM within the approach to validation as the current wording in PIC/S Annex 15 is viewed to be transitory with the next update reflecting a risk based approach.

5.5.6 CPV applications are typically adaptive (learning) systems, where the process design involves a design space, the application of PAT and/or MSPC. The multivariate mathematical models used for this purpose also need to be validated. In addition, it is necessary to periodically review the current control strategy. This may happen within the frame of ongoing process verification (see section 5.6)

5.5.7 For market release of batches where CPV was applied, the principles outlined for prospective validation in section 5.4 should be applied as feasible.

5.5.8 The **hybrid approach** to process validation (i.e. validation of parts of the process according to the traditional approach and other parts by applying CPV) may be applied where experience with and level of understanding of the process support the partial application of CPV. This knowledge may have been gained not only from quality-by-design development of the process but also from a well-documented manufacturing history demonstrating the variabilities of the process.

Accordingly, the hybrid approach may also be applied to legacy products initially validated using the traditional approach and for process validation of changes made to the process.

5.6 Ongoing (or Continued) Process Verification (OPV)

5.6.1 OPV should be initiated for every manufacturing process after conclusion of the initial process validation and pursued over the entire product lifecycle up until manufacturing of the product is discontinued.

5.6.2 Sampling and testing requirements during the OPV stage should be established based on risk assessment. For higher risk products, it may be necessary to conduct sampling at validation levels until enough confidence is gathered with respect to process capabilities. Sampling and testing requirements may also be gradually reduced, based on statistical analysis, from validation levels to standard batch release testing requirements.

5.6.3 The obligation to perform OPV exists irrespective of which approach was taken for the initial validation. OPV has taken the place of periodic revalidation and ensures that manufacturing processes should remain in a state of control.

5.6.4 To obtain information about process performance, a monitoring programme should be established where product quality is monitored, and potential adverse process trends can be promptly recognised. Regular trending should be capable of detecting adverse trends resulting from planned changes, from unnoticed or incremental changes, and from special causes of variability. The parameters and material attributes to be closely monitored and trended should be identified through risk assessment.

Additional sources of information which provide additional insight into the state of process control such as customer complaints, recalls, relevant deviations, etc. should be available from the quality system. For more information, see the Process Performance and Product Quality Monitoring System in ICH Q10

(Section 3.2.1). Effective linkage between the quality system and OPV should be established.

As a result of the risk assessment, it may be necessary to implement (temporarily) further controls, in addition to the data which are already collected routinely. The need to perform additional controls is more likely to be required when less information about a process is available (i.e. at the beginning of the product and process lifecycle) or when an adverse trend is suspected.

Overall, the effort required for the monitoring programme should be in relation to the likelihood of varying CQAs and the level of harm such variations may cause to patient health.

Accordingly, the level of sophistication of the methods used for trending and other kinds of statistical metrics should be aligned to the required confidence in the conclusions.

5.6.5 Results of the OPV programme should be reported on a regular basis. The reporting period should be defined based on risk considerations but normally should not exceed one year. However, there may be specific circumstances where the period should be extended to illuminate trends due to slow process drift or where products are manufactured infrequently. Conversely, a shorter period could be justified for high volume products, near term adverse trends, high severity defects or other indirect quality system issues not directly linked to the product. The report should comprise a conclusion whether the process is still considered to be in a state of control, and any recommendations to improve the process design, the routine control strategy, the design of CPV (as applicable), or the OPV monitoring programme itself. Objective statistical tools such as Cpk and Ppk should be used wherever possible.

5.6.6 To avoid redundant compilation of data, it is recommended OPV reports are designed in a way that they may be used as a reference for the periodic Product Quality Review (PQR) to demonstrate the validated state of the process.

5.7 Revalidation

5.7.1 All changes to manufacturing processes should be assessed for their impact on product quality and the validated state.

5.7.2 The expectations expressed in sections 5.2, 5.3, 5.4 and 5.5 also apply to revalidations, as far as possible. Any changes should be assessed for regulatory impact.
Depending on how much relevant information is available from the previous production history, the risk assessment may yield a result that reduces the scope for the revalidation compared to the initial validation; validating with fewer validation runs than the previous validation (in the case of a traditional approach), using a bracketing approach, and/or using concurrent process validation can be considered, especially if the revalidation is augmented by appropriate additional testing as part of the OPV programme, thereby monitoring the impact of the changes on the state of control of the process.

5.7.3 The discontinuation of a manufacturing process (and thus the completion of the lifecycle for that process) should be reflected in the VMP.

6. OTHER QUALIFICATION AND VALIDATION TOPICS

6.1 Verification of Transportation

6.1.1 Due to the global nature of supply chains for medicinal products it is of the utmost importance that finished products, intermediate bulk products, semi-finished product, API and samples should be transported in a manner which maintains the appropriate product storage conditions and prevents potential degradation or microbial contamination of the product. These requirements are important for both international and national shipments.

6.1.2 Many variables, often unpredictable, can affect international and domestic shipments of pharmaceutical products. Manufacturers should perform a risk assessment of known variables (weather, customs delays, staff shortages, breakdown etc.) that may impact shipments. As new, previously unknown variables are discovered, these should be incorporated into an updated risk assessment.

6.1.3 Local transportation routes are generally shorter and can often be more predictable based on historical weather patterns or the use of air conditioned or cold chain vehicles; however, risk assessments must still be performed.

6.1.4 It is important therefore from both a national and international perspective to understand the transportation route, in a high level of detail, from when the product leaves the manufacturing site until it arrives at the distribution site, or site of further processing or other distribution sites within the supply chain. The transport route should be formally documented and verified before use by execution of a test protocol. A report should document any issues or delays or proposed improvements.

6.1.5 This level of detail is important to ensure that a detailed risk assessment can be performed, appropriate mitigating actions taken, and appropriate agreements put in place with transport providers.

6.1.6 Environmental factors such as temperature, humidity, light, vibration (causing compaction in powders for inhalation, or particle size segregation which may be critical especially for poorly soluble APIs used in oral solid dose forms) may be important and need to be considered.

6.1.7 Loading of the container to ensure adequate air circulation within the container is important to prevent mould growth with adequate strapping of goods to ensure that the loading pattern in the container does not change.

6.1.8 Following risk assessment (6.1.2 above), data loggers or other similar devices may be required to be placed in a shipment. Where goods are shipped by air, consideration should also be given to having one data logger per pallet if there is a risk of pallets being separated. When data loggers are used, the location of each device within the shipment, traceability of each device to the data

collected, and the procedures to download and ensure the integrity of the data should be described in the shipping study protocol and verified before approval of the report. Data loggers should be calibrated at an appropriate frequency and have sufficient battery life for the expected shipping duration. Where advanced devices such as Radio Frequency Identification (RFID) are used, qualification of the system will be required.

6.1.9 Samples are often preselected by the manufacturing site and sent separately to the batch. The inclusion of data loggers should be based on a risk assessment to ensure that the samples received at the testing site are exposed to the same environmental conditions and therefore representative of what was experienced by the main batch during transport.

6.2 Validation of Packaging (Solid Dose Products only)

6.2.1 Some of the most common primary packing used for solid dosage forms are blisters, bottles, sachets, and tubes. These presentations are primarily designed to limit the environmental exposure of the product and reduce the potential for defects from physical damage. Blister and sachet packaging solutions often require complex packaging equipment and any failures in container integrity can have a significant impact on product stability. It is therefore important to discuss validation of the packaging process. Note: Packaging validation of other product types such as sterile product container integrity is covered in the PIC/S document PI 007 *Recommendation on the Validation of Aseptic Processes*.

6.2.2 Similar to the processes mentioned above, it is important to identify the critical process parameters through risk assessment and prepare a validation protocol reflecting the outcome of the risk assessment.

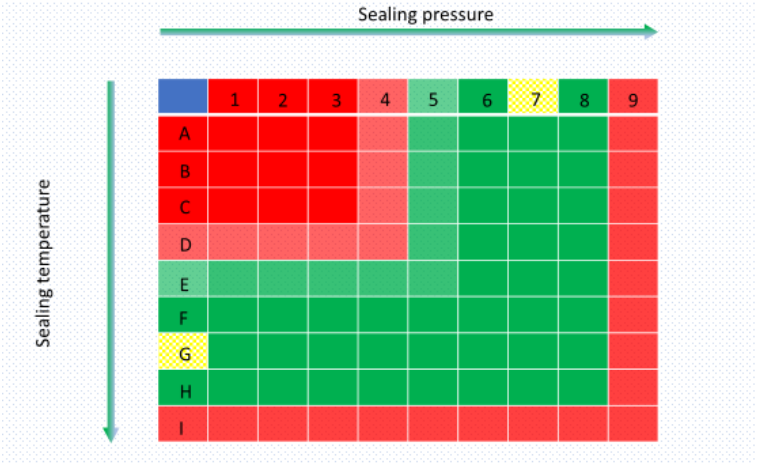
6.2.3 The principal critical parameters influencing integrity of a blister and sachet are usually sealing pressure, sealing temperature and speed of the machine. It is therefore important that the relationship between these factors and sealing integrity is determined. Sealing integrity is usually confirmed by submerging the blisters/sachet in a coloured dye batch and observing for leaks in the blister/sachet after pressure and vacuum is applied. Note: The use of pressure and vacuum is a more sensitive test than vacuum alone. An example of a typical blister/sachet validation is presented below.

6.2.4 A pre-validation exercise should therefore seek to vary pressure, temperature with the machine speed kept constant to determine the impact on the integrity of the blister or sachet. The validation is then repeated at various machine speeds and the range which produces an effective seal determined. It is important that testing covers a wide parameter range so that the selected parameters can be confirmed to be within a ‘optimum range’ and not close to the point of failure. Figure 2 is presented below which outlines this approach. At low sealing temperatures (A-D) and low sealing pressure (1-3) all blisters/sachets are not integral as indicated by the red area. As the sealing temperature (E) and pressure (5) are increased further, some of the integrity tested blisters will start to pass the integrity test but there will still be some failures. As the pressure (6 – 8) and temperature (F-H) is increased all blisters tested will be integral. Further increases in pressure (9) and temperature (I) will start to result in some blisters failing. The optimum pressure and temperature

are therefore 7 and G respectively which are in the middle of the green safe zone and marked in yellow.

6.2.5 The influence of potential exposure to heat during the packaging process should also be considered following stoppages when passing product through a blistering machine or through a shrink wrap tunnel several times.

Figure 2: Pre-validation Exercise Example (see 6.2.4)



6.3 Qualification of Supporting Utilities

6.3.1 Common supporting utilities used in manufacturing plants are water, electricity, steam, air, vacuum, ventilation systems, gas supplies (e.g. nitrogen). Generally, validation efforts should be directed towards utilities which are in direct contact with the product. Utilities which have no direct product impact only require to consistently meet a specification depending on their specific use (e.g. steam for heating vessels, potable water used for the initial rinsing of equipment). Risk assessments should include failure modes which may result on a direct product impact.

6.3.2 The qualification approach (URS, FAT, SAT, IQ, OQ and PQ) used in previous sections of this document apply to supporting utilities. This section will concentrate on some of the differences required when performing a PQ for supporting utilities and the additional risk assessments which may be required for certain supporting utilities.

6.3.3 Water is commonly received directly from the mains supply or stored in tanks on site and further processed through various treatment steps to produce either deionised, purified, water for injection or ‘process’ water (as required in the specific site specification).

6.3.4 In some countries, there may be no direct water supply and water is supplied to the manufacturing site by tanker. Tanker sourced water is potentially very difficult to qualify due to potential variations in the sourcing of the water, use of different tankers, and higher risk of contamination. Greater emphasis must

therefore be placed on procedural controls developed from the initial risk assessment to include holding times.

6.3.5 Specific procedural controls could include: technical agreements with the tanker company and/or water supplier, specifying one specific water source e.g. borehole rather than river water, controlling activities which can be performed around the borehole, specifying dedicated tankers for water use only, specifying the frequency and type of tanker and storage tank cleaning, specifying the chemicals used for the tanker internal coating and materials of construction, and on-site supervision of the borehole.

6.3.6 Water supply quality will be strongly influenced by annual seasonal variations which presents different challenges to the treatment process. Consequently, PQ should normally extend over a full year so that any seasonal variations in the mains water supply and any additional challenge to the water generation systems in the facility can be assessed. A typical purified water qualification would normally be performed in three phases: the first phase involves extensive chemical and microbiological testing of all user points to identify any significant issues for 1 - 4 weeks followed by phase 2 where testing frequency and the number of tests would be reduced based on risk assessment principles for around 4-12 weeks followed by extended testing for around 4 – 12 months.

6.3.7 Electrical supply can be interrupted without warning and the impact on the safe operation of the facility and protection of product quality should be considered using appropriate risk assessment tools. Any mitigating measures taken such as the installation of back-up generators and uninterruptable power supply (UPS) should be tested during qualification and at appropriate intervals thereafter based on risk.

6.3.8 Steam can be used in pharmaceutical manufacture for supply to jacketed equipment for heating or for use in autoclaves for sterilisation as two examples. It may also be used for general use, such as in HVAC units or for general heating of the building.

6.3.9 Steam used for sterilisation purposes (e.g. in an autoclaves, SIP, etc.), requires appropriate quality (e.g. clean steam) due to its contact with equipment and/or components used in sterile manufacture. Factors such as the quality of the stainless steel used in the generation and distribution pipework and regular quality testing of user points for non-condensable gases, superheat and dryness as well as chemical testing in accordance with the water for injection (WFI) monograph need to be considered.

6.3.10 Conversely, a lower steam quality could be used for heating a jacketed vessel or used in a heat exchanger where there is no product or component contact, however, the potential failure modes of the barrier between the steam supply and the finished product should be assessed in a risk assessment and appropriate mitigation introduced. This may include the use of a double skinned heat exchanger, considering the pressure differential between the product and the steam supply to ensure that any leaks would be outward from the product (higher pressure) to the steam supply (lower pressure) or pressure testing or physical examination at appropriate intervals.

6.3.11 The PQ of steam systems should ensure that all user points are sampled for critical parameters as indicated above if used for autoclaving of sterile components or for other functional parameters depending on the use of the steam.

6.3.12 Where the steam generating system supplies multiple equipment it is important that the capacity of the system to supply multiple equipment operating concurrently is confirmed during qualification. If additional equipment requiring a steam supply is added, the capacity of the current steam generation system should be evaluated and requalified as necessary once the new equipment is operational.

6.3.13 Inert gases, including Nitrogen, are commonly used as a product contact material to protect finished products from degradation by oxygen and therefore it is important that the nitrogen generation system if used and the distribution system do not impact the quality of the nitrogen used. Any nitrogen bottle changeover systems should be qualified and alarmed to ensure a constant supply of nitrogen when required.

6.3.14 Similarly, compressed air generation and distribution systems should be installed using materials which do not generate particulates or equipment which introduces oil, other hydrocarbons, microorganisms, or humidity into the distribution system. All gas systems should be robustly cleaned before use. Filters should be installed before the point of use, if required by the risk assessment, and gas supplied at the point of use should be tested for the absence of contaminants.

6.3.15 The integrity of distribution pipework and the integrity of any online filters checked before and after replacement should be confirmed as part of qualification.

6.4 Validation of Test Methods

6.4.1 Test methods may be required for raw materials, intermediates, finished product testing and during qualification and validation. Irrespective of use, all test methods should be validated (or verified for a pharmacopeia method). It is not intended to provide full details on the validation/verification of test methods in this document as this is already well documented and further details can be found in the references listed below.

- ICH Q2 (R2) *Validation of analytical procedures*
- *Analytical procedures and method validation for drugs and biologics*- FDA Guidance for Industry
- *Guidelines on validation – Appendix 4 - analytical method validation* – WHO

6.4.2 Prior to testing of finished products for absence of objectionable organisms or for a qualitative assessment of microbial growth (viable count), the suitability of the test method should be confirmed to ensure that the product tested itself does not have an antimicrobial effect which could mask the detection of any microbial growth in the product. If an antimicrobial effect is found, the test method should be modified. Modification may include, for example, increasing the volume of

diluent or culture media, incorporating neutralising agents, membrane filtration or a combination of the above methods.

6.4.3 Similarly, microbial testing of surfaces as part of an environmental monitoring programme, may be influenced by any residues of sanitising agents present on the surface and by neutralising agents added to the media. Validation is required to ensure that the results are not affected.

7. CLEANING VALIDATION

7.1 Principle

7.1.1 Finished products and APIs can be contaminated by other finished products or APIs, by cleaning agents, by micro-organisms or by other materials (e.g. by undesired by-products of partial or incomplete reactions or by inadequately recovered/recycled solvents). Measures to reduce potential contamination of APIs and finished products should be established using a documented quality risk management approach. A cleaning validation program will normally be an essential part of the contamination control strategy, especially in facilities where the same equipment is used to manufacture different products.

7.1.2 Cleaning validation is performed to demonstrate that the cleaning process will consistently reduce the possibility of chemical and/or microbial contamination (including process bioburden) of an API or finished product manufacturing process. Cleaning validation provides documented evidence that an approved cleaning process will reproducibly remove any residues (whether microbial or product residue or cleaning agent residue) in the equipment to below scientifically set maximum allowable carry-over (MACO) levels. For low health based exposure limit (HBEL) products a required level of consistency may not be achieved using manual cleaning and dedicated parts or automation of cleaning should be considered or verification at each product changeover should be conducted.

7.1.3 Validation of cleaning to achieve a minimum acceptable bioburden level is especially important for biological products where multiple processing steps, sampling after key process steps, and long process times increase the risk of microbial contamination and the bioburden challenge to the final aseptic filtration step.

7.1.4 Cleaning verification refers to the assessment of equipment cleanliness by analytical or other testing and is used throughout the cleaning lifecycle. Cleaning verification is used to verify that individual equipment has been appropriately cleaned and can be used whilst cleaning validation is ongoing or for routine verification of manual cleaning which cannot be validated, when automated cleaning is not possible.

Cleaning verification studies are used to:

a) ensure equipment involved in the manufacture of development or other non-commercial products have been appropriately cleaned — Note that development product should not be introduced into equipment/facilities used to manufacture commercial product or product for clinical trials in humans

without a thorough assessment of the risks and a robust verification program;
b) evaluate that equipment has been appropriately cleaned during the execution of the validation study; and
c) provide confidence that equipment has been appropriately cleaned and can be cleaned in a reproducible manner — this is an important consideration with manual cleaning procedures for products with low HBEL values.

7.1.5 A cleaning validation program will consist of three elements:

a) Ensure that the proper effort is applied to the development of cleaning processes where critical cleaning parameters will be identified, and cleaning processes adequately designed and controlled to ensure that they are conducted in a consistent and reproducible manner;
b) Conduct a cleaning validation study, which involves performing a predetermined number of cleaning verification assessments, to confirm that the cleaning procedures can consistently and effectively clean the equipment; and
c) Perform ongoing evaluation of any manual or automatic cleaning process after the completion of the validation study to ensure it remains within a state of control.

7.1.6 The amount and nature of cleaning validation and verification requirements should be established using a documented quality risk management assessment.

7.2 Purpose and Scope

7.2.1 These recommendations describe the validation of cleaning procedures for the removal of contaminants associated with the previous products or cleaning agent residues.

7.2.2 These recommendations apply to the manufacture of finished products and provide supplementary, optional guidance for APIs.

7.3 General

7.3.1 The extent of any cleaning program should be dependent upon a toxicological risk assessment (e.g. based on HBEL values). The risk assessment should then be used to determine the operational and technical controls required to deliver a validated cleaning process.

7.3.2 Cleaning validation studies will normally focus on product contact surfaces but should also evaluate the cleaning of non-contact parts from which residual product may migrate. Examples of such parts include seals, flanges, mixing shafts, oven fans, heating elements, etc. These should be identified via a practical risk-based study using the HBEL value to determine the extent that migration of product is a risk to contamination of a future product.

7.3.3 Cleaning procedures for product changeover of all products should be fully validated following coupon testing of different surfaces and acceptable recovery.

Cleaning validation studies should, at a minimum, be started when commercial production is initiated. They may, however, be initiated during development or prior to process validation once the cleaning process has been fully defined and if the manufacturing process/formulation are equivalent to the intended commercial production.

It is understood that it may take time to manufacture the required number of batches to confirm cleaning validation. In addition, it is anticipated that full-scale equipment may not be used in the production of development or trial batches.

a) Quality risk management principles should therefore be used to determine whether release of equipment, based on cleaning verification data, for the manufacture of other commercial products is acceptable before the cleaning validation phase is completed.
b) The risk of subsequent failures during cleaning verification runs should be taken into consideration (i.e. the impact on the overall validation program and risk of potential product contamination).
c) It is important to note that the same cleaning validation principles apply when conducting cleaning verification for development and trial batches.

7.3.4 Depending on product risk, it may be acceptable to conduct cleaning validation studies by evaluating a limited number of worst-case products. Manufacturers should have a documented justification to support the use of such a cleaning validation approach and of the actual identified worst-case product or products.

Examples of factors that can be considered in the assessment of worst-case products include HBEL values, cleaning difficulty, residue solubility in cleaning agents and water, the physical characteristics of the item being cleaned, and previous experience with similar products.

It may be necessary to select multiple worst-case products based on the factors under review. For example, an insoluble product with a high HBEL value may be the most difficult product to clean but not necessarily the worst case compared to a partially soluble product with a low HBEL value.

All products being evaluated under the worst-case approach should be identified.

7.3.5 Manufacturers should conduct cleaning validation on all equipment unless different items are an exact ‘like for like’ or any differences are justified as having no impact on the consistency of cleaning (this should be practically confirmed).

7.3.6 Cleaning procedures should be sufficiently detailed, controlled, and documented to increase the likelihood of them being reproducible.

7.3.7 Ensuring cleaning consistency is one of the biggest challenges for a manual cleaning program. The quality risk management evaluation should clearly identify the steps required to ensure both consistency in how the cleaning procedures are performed and the overall outcome of the cleaning program.

Factors to assure manual cleaning consistency include:

a) having adequately detailed instructions that document the sequence of cleaning steps including. equipment preparation or disassembly, the cleaning agent and concentration, how the cleaning agent is applied (e.g. soaking or scrubbing), cleaning tools (e.g. brushes), contact times, temperatures, rinsing techniques and rinse times, equipment drying, etc.;
b) ensuring operators are appropriately trained and/or qualified; and
c) ensuring that cleaning steps are adequately recorded and that any measuring devices, if used, are appropriately calibrated.

7.3.8 Automated cleaning procedures should also be appropriately controlled to ensure consistency by:

a) having adequately detailed procedures to describe the automated cleaning and any other relevant factors (e.g. equipment preparation or disassembly);
b) defining the cleaning sequence (including all temperatures, concentrations, cleaning agents, number of applications, valve openings, spray rates, pressures, and volumes);
c) establishing appropriate qualification, calibration, and maintenance programs;
d) monitoring critical control points and parameters with appropriate sensors and alarms — procedures should outline steps to be taken in response to alarms; and
e) ensuring cleaning recipes and data are appropriately controlled, reviewed and protected from accidental/intentional modification or deletion — data integrity should be designed into automated equipment and assessed before installation.

7.3.9 Manufacturers should also have adequate evidence to demonstrate:

a) The allowable time that equipment may remain dirty after production prior to cleaning and the allowable time cleaned equipment may be held before the next use.

b) The maximum allowable campaign length that will not impact product quality or cleanability. A manufacturing campaign involves manufacturing multiple lots of the same product with none or limited cleaning in between the batches; and

c) Factors for consideration in campaign length assessments include:
   - the potential for product build-up or residues that could impact product quality or processing ability,
   - microbiological controls, and
   - the impact of the longer production time on the cleaning process effectiveness.

   Note that campaign lengths should normally be defined by time and the number of batches.

7.3.10 Starting materials sourced from different suppliers may have different physical properties and impurity profiles. Such differences should be considered when

designing and validating cleaning procedures, as the materials may behave differently.

7.3.11 Any failures in cleaning during or post validation should be recorded, investigated and the impact on validation and verification determined. This should include all visual inspection failures identified, including the initial second person check after operators have completed manual cleaning.

7.3.12 Manufacturers should implement remediation actions if a cleaning process fails intermittently. Examples of remediation actions include reviewing the cleaning process and potentially improving cleaning procedures or reassessing the risk of cleaning failure and incorporating further mitigation such as equipment/facility dedication. Continued cleaning failures and/or testing until clean (i.e. continually cleaning and testing until acceptable results are achieved) are not acceptable.

7.4 Documentation

7.4.1 The starting point for any cleaning validation programme is a risk assessment that determines the scope, depth, breadth, and effort required for the programme.

7.4.2 A cleaning validation protocol is required to define the procedure for the cleaning validation exercise which should include the following:

a) the objective of the validation;
b) responsibilities for performing and approving the validation study;
c) a description of the equipment to be used;
d) the interval between the end of production and the beginning of cleaning;
e) the cleaning procedures to be used for each product, each manufacturing system, or each piece of equipment;
f) the number of cleaning cycles to be performed consecutively in order to prove the consistency of the method;
g) sampling procedures, including the rationale for why a specific sampling method is used;
h) clearly defined sampling locations and the rationale for selection;
i) data on recovery studies where appropriate;
j) analytical methods including the limit of detection and the limit of quantification for those methods;
k) the acceptance criteria, including the rationale for setting the specific limits; and
l) other products, processes, and equipment for which the planned validation is valid according to a “bracketing” concept, if applicable.

7.4.3 The cleaning validation protocol and report should be approved by Production, Quality Unit and other appropriate departments. It is important that management allocate adequate resources to enable the validation study to be successfully completed.

7.4.4 A final validation report should be prepared and approved by appropriate departments. The conclusions of this report should state if the cleaning process has successfully met the acceptance criteria and include any limitations or learnings during the validation study. The report should also include any requirements for ongoing verification and revalidation.

7.4.5 Records should be adequately detailed to provide evidence of completion of key steps and should be kept of all cleaning activities performed so that the following information is readily available:

a) the area or equipment cleaned;
b) the person who carried out the cleaning;
c) when the cleaning was carried out;
d) the SOP used in the cleaning process;
e) the product which was previously processed on the equipment being cleaned; and
f) any data/printouts recorded/obtained during the cleaning.

7.4.6 The cleaning record should be signed by the operator who performed the cleaning, by any personnel who supervised the cleaning and, by the personnel who visually inspected the equipment after cleaning had been completed.

7.5 Personnel

7.5.1 The level of required training and oversight should be assessed using quality risk management principles. For example, manual cleaning processes are considered inherently variable and will require qualification of personnel and additional oversight in accordance with quality risk management principles to ensure that as much variability has been removed from the cleaning processes as possible.

7.5.2 Personnel involved in the execution of a cleaning validation study should also be fully trained. For example, there should be clear evidence that personnel conducting swabbing of plant equipment will do so in the same manner performed during analytical recovery studies.

7.5.3 Personnel who perform cleaning post validation should be trained to follow validated cleaning procedures and records should be available for all training carried out.

7.6 Equipment

7.6.1 The design of equipment should be carefully examined following a procedure that describes how this will be conducted. Critical areas (those hardest to clean) should be identified, particularly in large systems that employ semi-automatic or fully automatic clean-in-place (CIP) systems. Parts of equipment that need to be dismantled for cleaning should be identified. Such evaluations should be conducted using equipment drawings and practical evaluations of equipment construction.

7.6.2 Dedicated equipment may be required for products which are difficult to remove (e.g. tarry or gummy residues in bulk manufacturing), for ancillary equipment which is difficult to clean (e.g. bags for fluid bed dryers, screens, sieves), or products with a high safety risk as identified during toxicological evaluation (e.g. products with a very low HBEL value).

7.7 Microbiological Aspects

7.7.1 The existence of conditions favourable to the reproduction of microorganisms (e.g. moisture, temperature, crevices, and rough surfaces) and the impact of long storage times should be considered. The aim should be to prevent objectionable types or levels of microbial contamination.

7.7.2 The storage conditions of equipment before cleaning and the time between cleaning and equipment re-use should be considered for the validation of cleaning procedures. This is to provide confidence that routine cleaning and storage of equipment does not allow microbial proliferation.

7.7.3 In general, equipment should be stored dry, and stagnant water should not be allowed to remain in equipment.

7.8 Visual Inspection

7.8.1 Visual inspection is a qualitative method to determine equipment cleanliness and involves the inspection of equipment for the absence of visible residue and foreign material. It is an important element of a cleaning program to ensure that cleaning is conducted appropriately and is effective. Note that some products may leave residues which only show up when the equipment has dried out and therefore visual inspection should always be conducted once the equipment has dried.

7.8.2 Visual inspection should be conducted and documented following all cleaning activity. Any visual inspection failures should be documented in the Quality System and investigated. The acceptance criteria for visual inspection is visually clean. Visually clean is the minimum standard expected, however, a comprehensive cleaning validation program will couple the performance of the visual inspection with the results of product surface or rinse sampling obtained with a validated analytical method with a sensitivity below the cleaning residue limit.

7.8.3 When scientifically justified to use visual inspection as the criteria to determine the cleanliness of equipment, an organisation should establish the threshold at which product residues are readily visible. Visual inspection will likely not be appropriate when lower HBEL products are manufactured and/or visual thresholds are nearer to the required safety limit. The approach should take into the account the ability to visually inspect the equipment, for example, under the lighting conditions and distances observed in the production areas. This determination is an important factor in the quality risk management process. Product residues which are not visually detectable below the safety limit may require cleaning verification at each product changeover.

7.8.4 Visual inspection should only be conducted by appropriately qualified personnel using suitable lighting conditions and background. The level of training and qualification should be established based on a risk assessment.

7.8.5 Procedures should be available which clearly outline how visual inspection is to be conducted. The procedures should include disassembly instructions, requirements to use an appropriate light source or mirror or potentially a borescope and instructions on how to assess difficult areas.

7.9 Sampling

7.9.1 Samples should be taken according to the cleaning validation protocol.

7.9.2 There are two methods of sampling that are generally accepted, direct surface sampling (swab method) and indirect sampling (use of rinse solutions). Swab sampling is generally considered to be more effective than rinse sampling and should be employed if feasible (i.e. per equipment design or if equipment can be dismantled). A combination of the two methods should be employed when the accessibility of equipment does not allow sufficient direct surface sampling.

It should be noted that rinse samples will result in an averaging of results so areas of high residual products will not be identified if the rinse is obtained from a large area.

a) Direct Surface Sampling (Swab/Wipe Method)

i. The direct surface sampling method should specify the sampling solvent, swab/wipe material to be used, sampling location(s), and the sampling technique. It is important to demonstrate the percentage of residues that can be recovered from all the applicable materials being tested (plastic, silicon, stainless steel etc.) using the specified direct surface sampling method. The recovery should be at an appropriate level to ensure residues can be successfully determined. A correction factor to account for incomplete recovery may be required based on or as demonstrated through swab recovery study/method validation.
ii. Direct surface sampling should be conducted at the hardest to clean as well as representative areas of the equipment. The hardest to clean areas should be selected based on a documented evaluation of the equipment including items such as material accessibility, equipment geometry, potential for residue accumulation and materials of construction.
iii. Microbial surface sampling should adopt similar principles to those mentioned above using sterile components.

b) Rinse Samples

i. Rinse samples allow sampling of large surface areas or inaccessible areas of equipment that cannot be routinely disassembled (e.g. inside tubing). However, consideration should be given to the solubility of the contaminant and the risk that localised contamination may be diluted.
ii. Studies should be performed to demonstrate the percentage of residue that the rinse method can recover from all materials of construction used in the production process. The studies should fully represent the rinse method used in production.
iii. A direct measurement of the product residue or contaminant in the relevant solvent should be made when rinse samples are used as part of validation of the cleaning process.

7.10 Detergents

7.10.1 The effectiveness of cleaning procedures to remove detergent residues should be evaluated. Acceptable limits should be defined for the level of detergent remaining after cleaning and ideally, no residues should be detected.

7.10.2 The composition of any detergents used should be known. If this information is not available, alternative detergents should be selected whose composition is defined (i.e. food grade use is a good indicator of suitability for pharmaceutical manufacture). The manufacturing site should ensure that the detergent manufacturing site or supplier notifies them of any critical changes in the formulation of the detergent.

7.11 Analytical Methods

7.11.1 All analytical methods used to measure product residues and contaminants (e.g. product active drug, degradants, and detergent residue) should be validated. The method should ensure integrity of the sample by defining the time from sample taking to start of analysis and any specific storage conditions required.

7.11.2 The analytical method validation should determine the limits of quantification and detection to ensure that the sensitivity of the analytical method is appropriate for the residue levels under consideration. Manufacturers should also ensure that the selectivity of the analytical method has been established in relation to potential degradants formed during the cleaning process.

7.11.3 The analytical methods should be challenged in combination with the sampling methods used, to show that the contaminants can be recovered from the equipment surfaces and to show the level of recovery as well as the consistency of recovery. This is necessary before any conclusions can be made based on the sample results.

7.11.4 It is generally appropriate that analytical methods used to detect residuals or contaminants are specific for the substances to be assayed and provide a sensitivity that reflects the level of cleanliness determined to be acceptable by the manufacturer.

7.11.5 Non-specific analytical methods (e.g. TOC and conductivity) may, however, be used with appropriate justification in specific circumstances where there is significant interference from other constituents and the method cannot test for specific product residues. In such cases, organisations must assume that the testing result is entirely due to the target residue in such cases. Manufacturers should still demonstrate that the sampling method will provide adequate and reproducible recovery.

7.11.6 Microbial testing methods should be validated for pharmacopoeia and local isolates and recovery confirmed to meet acceptance criteria.

7.12 Establishment of Limits

7.12.1 The rationale for selecting limits for cleaning agent, microbial, or product residues should be formally documented and based on a consideration of the materials involved and their therapeutic dose, potency and toxicological characteristics, and be practical, achievable, and verifiable. See PIC/S PI 046 *Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities.* Although this guideline may be used to justify cleaning limits, such evaluations are not intended to be used to set limits at the level of the calculated HBEL.

7.12.2 Manufacturers should consider setting alert limits which can, for example, be based on historical limits and/or a statistical evaluation of past cleaning results.

7.12.3 Calculated cleaning acceptance criteria should be established for both individual equipment and for the total cumulative carry-over results from multiple shared equipment (i.e. the process train effect). The impact of contamination on unit doses should also be considered (e.g. in compression or primary packaging).

7.12.4 Manufacturers should not assume that a contaminant will be uniformly distributed through a batch or on equipment. For example, depending on the process, there is the possibility that residual contamination on a surface might only occur at the beginning of a batch. All calculations and acceptance criteria should evaluate the potential of non-uniform contamination (if applicable).

7.12.5 It is also important to consider any potential carry-over when assessing cleaning effectiveness. For example, cleaning processes may result in degradation products and such products may be toxic and/or difficult to remove.

7.12.6 Products with low HBEL values may require additional controls.

7.13 Maintaining a Validated Cleaning Process

7.13.1 Additional monitoring should be conducted after the completion of cleaning validation studies to ensure cleaning processes remain in a state of control. The frequency and scope of such monitoring should be established using quality risk management principles and may require analytical monitoring of each product change. Areas of special concern include:

a) low HBEL product,
b) manual cleaning processes,
c) products with maximum allowable carry-over levels that are below the limit of visual detection,
d) the amount of data available to provide cleaning process confidence, and
e) equipment and products with a history of failure and/or highly variable verification testing results.

Note: Continued cleaning verification will normally be required, in accordance with quality risk management principles, for low HBEL products that are manually cleaned.

7.13.2 Products for which maximum allowable carryover limits are below the limit of visual detection (incorporating a safety factor) should be subject to cleaning verification after every change-over (product to product). This is of special concern when manual cleaning procedures are applied.

7.13.3 Control of changes to validated cleaning procedures is required. Re-validation should be considered in response to equipment, process, or product changes (e.g. change in detergent, site water pressure, repeat failures in cleaning verification).

7.13.4 Re-validation and observation of personnel to confirm that the equipment is cleaned as per the procedures should also be considered at routine intervals and in line with QRM principles.

8. GLOSSARY

Definitions of terms relating to qualification and validation which are not given in the glossary of the current PIC/S and EU Guide to GMP, but which are used in the recommendations which comprise this document, are given below.

Acceptance criteria
The criteria assigned, before undertaking testing, to allow evaluation of test results to demonstrate compliance with a test phase of delivery requirement.

Bracketing approach
A science and risk-based validation approach such that greater emphasis is placed on the process validation of batches at the extremes of certain predetermined and justified design factors, e.g., strength, batch size, pack size rather than intermediate factors. The design assumes that validation of any intermediate levels is represented by validation of the extremes. 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 a validated status. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state. These specific objectives with respect to change control are aligned with the ICH Q10 change management system.

Cleaning validation
Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the previous product, by products of concern or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level and ensure microbial control.

Cleaning verification
The gathering of evidence through appropriate analytical methods after each batch/campaign to show that the residues of the previous product or cleaning agents have been reduced below the scientifically set maximum allowable carryover level.

Concurrent validation
Validation carried out in exceptional circumstances, if there is 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)

Coupon testing
A recovery test conducted on a small sample of product contact equipment surface which is identical to the material of construction and the finish of the surface of the equipment. This testing is usually performed during the development of a cleaning validation method. Coupon testing may also be used to determine the level at which residues become visible or to establish the appropriateness of the cleaning agent on the equipment surface.

Critical material attribute (CMA)
Property of a raw or intermediate material whose variability has an impact on a critical quality attribute or on process performance and therefore should be monitored or controlled to ensure the process produces the desired quality.

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, supporting utilities, systems and equipment is suitable for the intended purpose.

Design space (DS)
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 a regulatory 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 performance and documentation of tests to ensure that equipment (such as machines, measuring equipment) used in a manufacturing process, are appropriately selected, correctly installed and work in accordance with established specifications.

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

Limit of detection
The lowest amount of analyte in a sample which can be detected by a test method but not quantitated as an exact value. The Limit of Detection is mostly a parameter of limit tests.

Limit of quantitation
The lowest amount of analyte in a sample which can be quantitatively determined by a specific test method with defined precision and accuracy under the stated experimental conditions.

MSPC
Multivariate Statistical Process Control Charts are a method which is used to detect shifts in the relationship (covariance) between several related parameters.

Ongoing (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, supporting utilities, systems, and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

Performance qualification (PQ)
The documented verification that systems and equipment, can perform effectively and reproducibly, based on the approved process method and product specification.

Piping & Instrumentation diagrams (P&IDs)
Engineering schematic drawings that provide details of the interrelationship of equipment, services/utilities, material flows, plant controls and alarms. The P&ID also provide the reference for each tag or label used for identification.

Plant functional specifications
Specifications that document functions, standards and permitted tolerances of systems (plant) or system components (equipment) and which define the operating capabilities of the equipment.

Process capability study
A process capability study is a statistical method that compares process information (e.g. X and s) to the upper and lower specification limits.

Process capability index (Cpk, Ppk)
A process capability index Cpk is a measurement of the potential of a process to meet specification:

$$= \frac{X - LSL}{3s}$$

$$\text{or} \quad \frac{USL - X}{3S}$$

where

LSL = Lower specification limit
USL = Upper specification limit
X = Mean
s = Standard deviation

Ppk is an index of process performance which tells how well a system is meeting specifications. This index also considers how well the process is centred within the specification limits.

If Ppk is 1.0, the system is producing 99.73% of its output within specifications. The larger the Ppk, the less the variation between process output and specifications.

If Ppk is between 0 and 1.0, not all process output meets specifications.

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.

Prospective validation
Establishing documented evidence that a process, procedure, system, equipment, or mechanism used in manufacture does what it purports to do based on a pre-planned validation protocol.

Qualification
Identification of facility, supporting utilities, equipment, and system attributes related to the performance of a function or functions and allocation of certain limits or restrictions to those attributes.

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)

Quality Target Product Profile (QTPP)
A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (ICH Q8)

Re-validation
Additional process validation to provide assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality.

Sensitivity
Capacity of the test procedure to record small variations in concentration of a component, with a defined degree of precision.

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 acceptable process performance and product quality. (ICH Q10)

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

User requirements specification (URS)
The set of owner, user, and engineering requirements necessary and enough to create a feasible design meeting the intended purpose of the system.

Validation Master Plan (VMP)
A document providing information on the manufacturer' 's qualification and validation work programme. It should define details of and timescales for the validation work to be performed. Responsibilities relating to the plan should be stated.

Validation protocol
A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment and decision points on what constitutes acceptable test results.

Validation report
Document reporting the validation activities, the validation data and the conclusions drawn.

Worst case
A condition or set of conditions encompassing upper and lower processing limits and circumstances, within SOPs, 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.

9. REVISION HISTORY

Date	Version Number	Reasons for revision
1 April 2000	PR 1/99-2	Copyright statement inserted; change in the editor's e-mail; new page numbering
30 July 2001	PI 006-1	Document adopted as a guidance document for inspectors by PIC/S Committee on 22 May 2001. As a result, the document reference number was changed. Other changes: "editor" (cover page), "document history", "introduction" (paragraphs on purpose and scope added), new page and paragraph numbering.
1 July 2004	PI 006-2	Change in the Editor's co-ordinates
25 September 2007	PI 006-3	Change in the Editor's co-ordinates
1 October 2026	PI 006-4	Up-date according to the revised chapters 3 and 5 and Annex 15 of the GMP Guide