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ANNEX 15 [1]

VALIDATION MASTER PLAN
DESIGN QUALIFICATION, INSTALLATION AND OPERATIONAL QUALIFICATION
NON-STERILE PROCESS VALIDATION
CLEANING VALIDATION

Introduction

Qualification and Validation should establish and provide documentary evidence that:

- the premises, the supporting utilities, the equipment and the processes have been designed in accordance with the requirements of GMP. This constitutes **Design Qualification or DQ.**

- the premises, supporting utilities and the equipment have been built and installed in compliance with their design specifications. This constitutes **Installation Qualification or IQ.**

- the premises, supporting utilities and the equipment operate in accordance with their design specifications. This constitutes **Operational Qualification or OQ.**

- a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. This constitutes **Process Validation or PV.** The term **Performance Qualification or PQ** may be used also.

Any aspect of, including significant changes to, the premises, the facilities, the equipment or the processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.

It is a requirement of GMP that each pharmaceutical company identifies what qualification and validation work is required to prove control of the **critical** aspects of their particular operation. Common sense and an understanding of pharmaceutical processing go a long way towards determining what aspects of an operation are critical.

The key elements of a qualification and validation programme of a company should be clearly defined and documented in a Validation Master Plan.

Qualification and validation can not be considered once-off exercises, for example, the start-up of a new manufacturing operation. An ongoing programme should follow its first implementation.

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[1] Draft 4, 17 September 1999

Commitment of the company to control change to premises, supporting utilities, materials, equipment and processes used in the manufacture of medicinal products is essential to ensure a continued validation status of the systems concerned. This commitment should be stated in the relevant company documentation, for example, the Quality Manual, Quality Policy Documents or the Validation Master Plan. As part of its Quality Management System the company should have a defined and formalised Change Control Procedure.

While the GMP Guide specifically identifies the responsibility of the Production and Quality Control departments, in practice, other departments, like Engineering and Research and Development as well as Contractors are usually involved in the programme.

It is the responsibility of the pharmaceutical company to define the respective responsibilities of its personnel and of external contractors in the qualification and validation programme. This should form part of the Validation Master Plan. However, the Quality Assurance function of a company should normally have a critical role in overseeing the whole qualification and validation process.

It is recommended that the validation programme be actively co-ordinated and managed by the company. To this end, validation teams are often formed with specific roles identified and assigned to individual team members. It is imperative that the most senior level of management within the company understands the personnel, time and financial resources required to execute a qualification and validation programme and commits the necessary resources to the work.

1. VALIDATION MASTER PLAN

1.1. Principle

1.1.1. Validation requires a meticulous preparation and careful planning of the various steps in the process. All work involved should be carried out in a structured way according to formally authorised standardised working procedures. Validation is characterised by:

- a multidisciplinary approach**:** validation requires the collaboration of experts of various disciplines such as pharmacists, technologists, metrologists, chemical analysts, microbiologists, engineers, experts on Q.A. validation etc..

- time constraints: validation work is submitted to rigorous time schedules. These studies are always the last stage prior to taking new processes, facilities into routine operation,

- costs: Validation studies are costly as they require time of highly specialised personnel and expensive technology.

The above factors require a well organised and structured approach that should be adequately described in a Validation Master Plan (VMP).

1.2 Purpose and Definition

1.2.1. The VMP should present an overview of the entire validation operation, its organisational structure, its content and planning. The core of the VMP being the list / inventory of the items to be validated and the planning schedule.

1.2.2. A Validation Master Plan is a document that summarises the firm's overall philosophy, intentions and approach to be used for establishing performance adequacy.

1.3. Scope

1.3.1. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in a VMP. This includes qualification of critical manufacturing and control equipment.

1.3.2. The VMP should comprise all Prospective, Concurrent, Retrospective Validations as well as Re-validations.

1.3.3. In case of large projects like the construction of a new facility, often the best approach is to create a separate VMP. (In such situations the VMP should be part of the total project management.)

1.4. Format and Content

1.4.1. The VMP should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but refer to existing documents such as policy documents, SOP's and validation protocols/reports.
The VMP should be agreed by management and requires regular updating.

1.4.2. A VMP should contain data on the following subjects / proposed chapters:

(a) an introduction: the firm's validation policy, general description of the scope of those operations covered by the VMP, location and schedule (including priorities);

(b) the organisational structure of all validation activities: personnel responsibility for the VMP, protocols of individual validation projects, validation work, report and document preparation and control, approval / authorisation of validation protocols and reports in all stages of validation processes, tracking system for reference and review, training needs in support of validation;

(c) plant / process / product description: provides a cross reference to other documents. A rationale for the inclusion or exclusion of validations, for the validation approach, the extent of validation and any challenge and or “worst case” situation should be included. Consideration can be given to the grouping of products / processes for the purpose of validating "worst case" situations. Where "worst case" situations cannot be simulated, the rationale for the groupings made should be defined;

(d) specific process considerations: characteristics / requirements of the plant / process etc. that are critical for yielding a quality product and need extra attention may be briefly outlined here;

(e) list of products / processes / systems to be validated: all validation activities comprised in the VMP should be summarised and compiled in a matrix format . Such matrix should provide an overview and contain:

- all items covered by the VMP that are subject to validation describing the extent of validation required [i.e. IQ, OQ and/or PQ]. It should include validation of analytical techniques which are to be used in determining the validation status of other processes or systems,
- the validation approach, i.e. prospective, retrospective or concurrent,
- the re-validation activities,
- actual status and future planning;

(f) key acceptance criteria: a general statement on key acceptance criteria for the items listed above;

(g) documentation format: the format to be used for protocols and reports should be described or referred to;

(h) required SOP's: a list of relevant SOP's should be presented;

(i) planning & scheduling: an estimate of staffing (including training needs), equipment and other specific requirements to complete the validation effort,.a time plan of the project with detailed planning of subprojects. This time plan could be included in the above mentioned matrix;

(j) change control: a statement of the company's commitment to controlling critical changes to materials, facilities, equipment or processes (including analytical techniques), should be included.

2. Design Qualification, Installation and Operational Qualification

2.1. Principle

2.1.1. A very important step within qualification is the correct design of equipment and ancillary systems for the intended use. Therefore qualification starts with the documented verification of the user requirements for an equipment and its ancillary systems. This process is called Design Qualification or DQ.

2.1.2. After the initial Design Qualification, Installation and Operational Qualification exercises assure through appropriate performance tests and related documentation and records that equipment and ancillary systems or sub-systems have been commissioned correctly and that all future operations will be reliable and within prescribed or specified operating limits.

2.1.3. These guidelines outline the principles and basic requirements for the Installation and Operational Qualification of systems or subsystems (equipment) including support systems used in the manufacture of all pharmaceutical products, including active pharmaceutical ingredients (APIs). The recommendations are intended to cover installation and operation of new or modified systems or sub-systems.

2.1.4. The detail and scope of a qualification exercise is in many respects related to the complexity of the equipment involved and the critical nature of that equipment with respect to the quality of the final product. Nevertheless, the basic principles should be adhered to whether it is the installation and operation of a simple piece of equipment or an autoclave.

2.1.5. The basic principles are as follows:

(a) The equipment should be correctly installed in accordance with an installation plan, as per supplier and any special (purchaser) requirements,

(b) The requirements for calibration, maintenance and cleaning developed as draft procedures should be reviewed and finally issued as authorised standard operating procedures (SOPs) as part of the SOP programme of the company,

(c) Operating requirements should be established and tests conducted to assure equipment is operating correctly, under normal and “worst case” conditions,

(d) Operator training requirements pertaining to the new equipment should be finalised and documented.

2.1.6. At various stages in a validation exercise there is need for protocols, documentation, procedures, equipment, specifications, acceptance

criteria for test results to be reviewed, checked and authorised.It would be expected that representatives of the main professional disciplines, e.g. Engineering, Research & Development, Manufacturing, Quality Control and Quality Assurance, involved in manufacture are actively involved in these undertakings with the final authorisation given by a validation committee or the Quality Assurance representative.

2.2. Installation Qualification (I.Q.) - Overview Statement

2.2.1. Installation Qualification is an essential step preceding the Process Validation exercise. It is normally executed by the Engineering group. The installation of equipment, piping, services and instrumentation is undertaken and checked to engineering drawings Piping & Instrument Diagrams, (P&IDs) and Plant Functional Specifications developed during the project planning stage. During the project planning stage, Installation Qualification should involve the identification of all system elements, service conduits and gauges and the preparation of a documented record that all installed equipment satisfies the planned requirements.

2.2.2. Identification and documenting of maintenance requirements for each installed item and the collection and collation of supplier operating and working instructions, maintenance and cleaning requirements, should form the minimum documentation for a satisfactory Installation Qualification.

2.3. Installation Qualification - Essential Elements

Installation of Equipment

2.3.1. The installation of equipment singularly or as a group (plant) should follow well defined plans. The plans will have been developed and finalised following progression through a number of design stages. The plans will normally be available and documented as Equipment Specifications, Plant Functional Specifications and Piping & Instrument Diagrams (P&IDs). During the design stage, an effective Change Management procedure should be in place. All changes to the original design criteria should be documented and after that, appropriate modifications made to Equipment Specifications, Plant Functional Specifications and Piping & Instrument Diagrams (P&IDs).

2.3.2. During the final phases of the design stage the facilities and equipment necessary for calibration requirements will need to be identified.

Calibration Requirements

2.3.3. (a) confirmation of calibration of calibrating equipment with reference to the appropriate national standard,

(b) calibration of measuring devices utilised in the Operational Qualification stage, where confirmation of calibration is unavailable,

(c) calibration of measuring devices related to installed equipment,

(d) identification of calibration requirements for measuring devices for the future use of the equipment.

Checking of Suppliers

2.3.4. For complicated or large pieces of equipment, a pharmaceutical manufacturer may elect to undertake a pre-delivery check of the equipment at the supplier's assembly facility, this pre-delivery check cannot substitute for the Installation Qualification. However, it is acknowledged that the checks conducted and documented at this stage may duplicate a number of the checks conducted at the Installation Qualification stage, hence, there could be a reduction in the scope of the Installation Qualification checks. If part of the Installation Qualification is performed by the supplier, the user should participate to the writing and implementing of the protocol and should get all the results at the end of the tests.

Checking at Users

2.3.5. Installation Qualification requires a formal and systematic check of all installed equipment against the equipment supplier's specifications and additional criteria identified by the user as part of the purchase specifications. At the Installation Qualification, all equipment, gauges and services should be given a serial (or other reference) number and a check conducted that the installed equipment (or plant) has been installed in accord with the current (approved) version of the Piping & Instrument Diagram (P&ID).

2.3.6. Confirmation of compliance of the operating criteria for the equipment, as installed, with the Plant Functional Specifications and Process Flow Diagrams should be documented.

Installation Qualification

2.3.7. At the Installation Qualification stage the company should document preventative maintenance requirements for installed equipment. At this stage new equipment and the preventative maintenance requirements should be added to the preventative maintenance schedule of the pharmaceutical manufacturer. Cleaning, including sanitisation and/or sterilisation requirements for the equipment, should be developed in draft documentation form from equipment supplier specifications and operating procedures. The draft cleaning documentation should be finalised following experience and observation at the Operational Qualification stage and then verified at the Performance Qualification stage.

2.4. Operational Qualification (O.Q) - Overview Statement

2.4.1. Operational Qualification is an exercise oriented to the engineering function, generally referred to as commissioning. Studies on the critical variables (parameters) of the operation of the equipment or systems will define the critical characteristics for operation of the system or sub-system. All testing equipment should be identified and calibrated before use. Test methods should be authorised, implemented and resulting data collected and evaluated.

2.4.2. It is important at this stage to assure all operational test data conform with pre-determined acceptance criteria for the studies undertaken.

2.4.3. It is expected that during the Operational Qualification stage the manufacturer should develop draft standard operating procedures (SOPs) for the equipment and services operation, cleaning activities, maintenance requirements and calibration schedules.

2.4.4. An effective change control procedure should be operational and encompass the whole project from the pre-planning stage through to the final acceptance of the Process Validation exercise.

2.5. Operational Qualification - Essential Elements

2.5.1. The conduct of an Operational Qualification should follow an authorised protocol. The critical operating parameters for the equipment or the plant should be identified at the Operational Qualification stage. The plans for the Operational Qualification should identify the studies to be undertaken on the critical variables, the sequence of those studies and 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 equipment will work (defined in design criteria and specifications).

2.5.2. Where applicable, simulated product may be used to conduct the Operational Qualification. Studies on the critical variables should include a condition or a set of conditions encompassing upper and lower processing or operating limits and circumstances; commonly referred to as "worst case" conditions. Such conditions should not necessarily induce product or process failure.

2.5.3. The completion of a successful Operational Qualification should allow the finalisation of operating procedures and operator instructions documentation for the equipment. This information should be used as the basis for training of operators in the requirements for satisfactory operation of the equipment.

2.5.4. Draft cleaning procedures developed at the Installation Qualification stage should be finalised after a satisfactory Operational Qualification exercise and issued as standard operating procedures (SOPs). Where applicable, these procedures should be validated as part of the Performance Qualification phase.

2.5.5. The completion of satisfactory Installation Qualification and Operational Qualification exercises should permit a formal "release" of the equipment/plant for the next stage in the validation exercise (Process Validation). The release should not proceed unless calibration, cleaning, preventative maintenance and operator training requirements have been finalised and documented. The release should take the form of written authorisations for both Installation Qualification and Operational Qualification.

2.6. Re-Qualification

2.6.1. Modifications to, or relocation of, equipment should only follow satisfactory review and authorisation of the documented change proposal through the change control procedure. Part of the review procedure should include consideration of re-qualification of the equipment. Minor changes should be handled through the documentation system of the preventative maintenance programme.

2.7. Qualification of Established (in-use) Equipment

2.7.1. While it is not possible to undertake the details of an Installation Qualification for established equipment nor the detailed approach for an Operational Qualification, nevertheless there should be data available that support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventative maintenance, operating procedures and operator training procedures for the use of the equipment should be documented and in use as standard operating procedures (SOPs).

3. NON-STERILE PROCESS VALIDATION

3.1. Principle

Process Validation is the means of ensuring, and providing documentary evidence that processes (within their specified design parameters) are capable of repeatedly and reliably producing a finished product of the required quality. The requirements and principles outlined in these guidelines are applicable to the manufacture and packaging of non-sterile pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and Re-validation.

3.2. General

3.2.1. Any manufacturing or packaging process will involve a number of factors that may affect product quality. These factors will be identified during the development of a product and will facilitate process optimisation studies. On completion of development and optimisation, Process Validation provides a structured way of assessing methodically the factors that impact on the final product.

3.2.2. It would normally be expected that Process Validation be completed prior to the manufacture of finished product that is intended for sale (Prospective Validation). Where this is not possible, it may be necessary to validate processes during routine production (Concurrent Validation). Processes which have been in use for some time should also be validated (Retrospective Validation).

3.2.3. In theory a validation exercise should only need to be carried out once for any given process. In practice however the process rarely remains static. Changes occur in components (raw materials and packaging materials), equipment is modified and the process environment cannot be assumed to remain as during the initial validation. A regular programme of re-validation is essential.

3.2.4. The company's policy and approach to Process Validation should be clearly defined.

3.3. Prospective Validation

3.3.1. During product development the production process should be broken down into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical factors/parameters that may affect the quality of the finished product.

3.3.2. A series of experiments should be devised to determine the criticality of these factors. Representatives from production, QC/QA, engineering, and in some cases research and development will normally be involved

in this process. These experiments may incorporate a challenge element to determine the robustness of the process. Such a challenge is generally referred to as a "worst case" exercise. The use of starting materials on the extremes of the specification may indicate the ability of the process to continue producing finished product to the required specification.

3.3.3. Each experiment should be planned and documented fully in an authorised protocol. This document will have the following elements:

(a) a description of the process,

(b) a description of the experiment,

(c) details of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with its calibration status,

(d) the variables to be monitored,

(e) the samples to be taken - where, when, how and how many,

(f) the product performance characteristics/attributes to be monitored, together with the test methods,

(g) the acceptable limits ,

(h) time schedules,

(i) personnel responsibilities,

(j) details of methods for recording and evaluating results, including statistical analysis.

3.3.4. All equipment, the production environment and analytical testing methods to be used should have been fully validated, (Installation/Operational Qualification). Staff taking part in the validation work should have been appropriately trained. In practice, Operational Qualification may be carried out using batches of actual product. This work may also fulfil the requirements of Prospective Validation. This approach to validation should not be adopted as a standard practice however.

3.3.5. Master Batch Documentation can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined.

3.3.6. Using this defined process (including specified components) a series of batches of the final product should be produced. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process. In practice, it may take some considerable time to accumulate this data.

3.3.7. It is preferred that the batches made should be the same size as the intended batch size for full scale production. This may not always be practical due to a shortage of available starting materials and in such cases the effect of the reduced batch size should be considered in the design of the protocol. A reduced batch size should correspond to at least 10 % of the intended batch size for full scale production. When full scale production starts, the validity of any assumptions made should be demonstrated.

3.3.8. During the processing of the batch/run, extensive testing should be performed on the product at various stages. Detailed testing should also be done on the final product and its package.

3.3.9. The batches/runs under validation should be documented comprehensively. The following items should be included in the validation report:

(a) a description of the process – Batch Processing/Packaging Records, including details of critical steps,

(b) a detailed summary of the results obtained from in-process and final testing, including data from failed tests. When raw data are not included reference should be made to the sources used and where it can be found,

(c) any work done in addition to that specified in the protocol or any deviations from the protocol should be formally noted along with an explanation,

(d) a review and comparison of the results with those expected,

(e) formal acceptance/rejection of the work by the team/persons designated as being responsible for the validation, after completion of any corrective action or repeated work.

3.3.10. Upon completion of the review, recommendations should be made on the extent of monitoring and the in-process controls necessary for routine production. These should be incorporated into the Manufacturing Formula and Processing Instructions or the Packaging Instructions or into appropriate standard operating procedures (SOPs). Limits, frequencies and actions to be taken in the event of the limits being exceeded should be specified.

3.3.11. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice and the Marketing Authorisation (if applicable). The premises used should be named on a Manufacturing Authorisation and this Authorisation should allow the manufacture/assembly of the particular type of product. The batch must be formally certified by a Qualified Person before release.

3.4. Concurrent Validation

3.4.1. In certain circumstances it may not be possible to complete a validation programme before routine production starts. In these cases it will be known in advance that the finished product will be for sale or supply. Circumstances where this is likely are, for example, when a process is being transferred to a third party contract manufacturer/assembler.

3.4.2. In addition there are many instances when it is appropriate to validate a process during routine production. Such instances are, for example, where the product is a different strength of a previously validated product, a different tablet shape or where the process is well defined.

3.4.3. It is important in these cases however, that the premises and equipment to be used have been validated previously and that the decision to carry out Concurrent Validation is made by appropriately authorised people.

3.4.4. Documentation requirements are the same as specified for Prospective Validation and the testing to be carried out in-process and on the finished product will be as specified in approved protocols. The completed protocols and reports should be reviewed and approved before product is released for sale or supply.

3.5. Retrospective Validation

3.5.1. There are many processes in routine use in many companies that have not undergone a formally documented validation process.

3.5.2. Validation of these processes is possible, using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. The steps involved in this type of validation still require the preparation of a specific protocol, the reporting of the results of the data review, leading to a conclusion and recommendation.

3.5.3. This type of validation exercise is only acceptable for well established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

3.5.4. The source of data for this validation may include batch documents, process control charts, maintenance log books, records of personnel changes, process capability studies (reflected in a CpK), finished product data, including trend cards, and storage stability results.

3.6. Re-validation

3.6.1. Re-validation provides the evidence that changes in a process and/or the process environment, introduced either intentionally or unintentionally, do not adversely affect process characteristics and product quality.

3.6.2. There are two basic categories of Re-validation:

(a) Re-validation in cases of known change (including transfer of processes from one company to another or from one site to another),

(b) Periodic Re-validation carried out at scheduled intervals, which are justified.

3.6.3. A system should be in place (refer to Validation Master Plan requirements) to ensure both situations are addressed. Documentation requirements will be the same as for the initial validation of the process, and in many cases similar protocols can be employed.

3.6.4. The definition of what constitutes a change to a process or process environment needs to be agreed. Guidance on this is given below.

3.6.5. The need for periodic Re-validation of non-sterile processes is considered to be a lower priority than for sterile processes. In the case of standard processes on conventional equipment a data review similar to what would be required for Retrospective Validation may provide an adequate assurance that the process continues under control. In addition the following points should also be considered:

(a) the occurrence of any changes in the master formula, methods or starting material manufacturer,

(b) equipment calibrations carried out according to the established programme,

(c) preventative maintenance carried out according to the programme,

(d) standard operating procedures (SOPs) up to date and being followed,

(e) cleaning and hygiene programme still appropriate,

(f) unplanned changes or maintenance to equipment or instruments.

3.7. Change Control

3.7.1. Change control is an important element in any Quality Assurance system. Written procedures should be in place to describe the actions to be taken if a change is proposed to a product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or support system operation.

3.7.2. All changes should be formally requested, documented and accepted by representatives of Production, QC/QA, R&D, Engineering and Regulatory Affairs as appropriate. The likely impact (risk assessment) of the change on the product should be evaluated and the need for,

and the extent of Re-validation discussed. The change control system should ensure that all notified or requested changes are satisfactorily investigated, documented and authorised.

3.7.3. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specification. Significant changes to processes which are likely to impact on product quality may need regulatory authority approval and the appropriate supporting data, obtained through re-validation, should be submitted by way of variation to the marketing authorisation. Products made by processes subjected to changes should not be released for sale without full awareness and consideration of the change by responsible staff, including the Qualified Person.

3.7.4. Changes that are likely to require Re-validation and might need to be submitted for Quality Assurance pre-approval and subsequently for regulatory approval, are as follows:

(a) changes of raw materials (physical properties such as density, viscosity, particle size distribution may affect the process or product),

(b) change of starting material manufacturer,

(c) changes of packaging material (e.g. substituting plastic for glass),

(d) changes in the process (e.g. mixing times, drying temperatures),

(e) changes in the equipment (e.g. addition of automatic detection systems). Changes of equipment which involve the replacement of equipment on a 'like for like' basis would not normally require a Re-validation,

(f) production area and support system changes (e.g. rearrangement of areas, new water treatment method),

(g) transfer of processes to another site,

4. Cleaning Validation

4.1. Principle

4.1.1. Pharmaceutical products and active pharmaceutical ingredients (APIs) can be contaminated by other pharmaceutical products or APIs, by cleaning agents, by micro-organisms or by other material (e.g. air-borne particles, dust, lubricants, raw materials, intermediates, auxiliaries). In many cases, the same equipment may be used for processing different products. To avoid contamination of the following pharmaceutical product, adequate cleaning procedures are essential.

4.1.2. Cleaning procedures must strictly follow carefully established and validated methods of execution. In any case, manufacturing processes have to be designed and carried out in a way that contamination is reduced to a pre-determined level.

4.1.3. Cleaning Validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing of pharmaceutical products.

4.1.4. Objective of the Cleaning Validation is the confirmation of a reliable cleaning procedure so that the analytical monitoring may be reduced to a minimum in the routine phase.

4.2. Purpose and Scope

4.2.1. These guidelines describe the validation of cleaning procedures for the removal of contaminants associated with the previous products, residues of cleaning agents as well as the control of potential microbial contaminants.

4.2.2. These guidelines apply to the manufacture of pharmaceutical products (final dosage forms).

4.3. General

4.3.1. Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts into which product may migrate. For example premises, seals, flanges, mixing shaft, fans of ovens, heating elements etc.

4.3.2. Cleaning procedures for product changeover should be fully validated.

4.3.3. Generally in case of batch-to-batch production it is not necessary to clean after each batch. However, cleaning intervals and methods should be determined.

4.3.4. Several questions should be addressed when evaluating the cleaning process. For example:

(a) at what point does a piece of equipment or system become clean?

(b) what does visually clean mean?

(c) does the equipment need to be scrubbed by hand?

(e) what is accomplished by hand scrubbing rather than just a solvent wash?

(f) how variable are manual cleaning processes from batch to batch and product to product?

(g) what is the most appropriate solvent or detergent?

(h) are different cleaning processes required for different products in contact with a piece of equipment?

(i) how many times need a cleaning process be applied to ensure adequate cleaning of each piece of equipment?

4.3.5. Cleaning procedures for products and processes which are very similar, do not need to be individually validated. It is considered acceptable to select a representative range of similar products and processes concerned and to justify a validation programme which addresses the critical issues relating to the selected products and processes. A single validation study under consideration of the “worst case” can then be carried out which takes account of the relevant criteria. This practice is termed "Bracketing".

4.3.6. At least three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.

4.3.7. Raw materials sourced from different suppliers may have different physical properties and impurity profiles. Such differences should be considered when designing cleaning procedures, as the materials may behave differently.

4.3.8. Control of change to validated cleaning procedures is required. Re-validation should be considered under the following circumstances:

(a) re-validation in cases of changes to premises, equipment, products or processes,

(b) periodic re-validation at defined intervals.

4.3.9. Manual methods should be reassessed at more frequent intervals than clean-in-place (CIP) systems.

4.3.10. It is usually not considered acceptable to "test until clean". This concept involves cleaning, sampling and testing, with repetition of this sequence until an acceptable residue limit is attained. For the system or equipment with a validated cleaning process, this practice of "test until clean" should not be required. The practice of "test until clean" is not considered to replace the need to validate cleaning procedures.

4.3.11. Products which simulate the physicochemical properties of the substance to be removed may be used exceptionally instead of the substances themselves, where such substances are either toxic or hazardous.

4.4. Documentation

4.4.1. A Cleaning Validation Protocol is required laying down the procedure on how the cleaning process will be validated. It should include the following:

(a) the objective of the validation process,

(b) responsibilities for performing and approving the validation study,

(c) description of the equipment to be used,

(d) the interval between the end of production and the beginning of the cleaning procedures,

(e) 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,

(g) any routine monitoring requirement,

(h) sampling procedures, including the rationale for why a certain sampling method is used,

(i) clearly defined sampling locations,

(j) data on recovery studies where appropriate,

(k) analytical methods including the limit of detection and the limit of quantitation of those methods,

(l) the acceptance criteria, including the rationale for setting the specific limits,

(m) other products, processes, and equipment for which the planned validation is valid according to a “bracketing” concept,

(n) when Re-validation will be required.

4.4.2. The Cleaning Validation Protocol should be formally approved by the Plant Management, to ensure that aspects relating to the work defined in the protocol, for example personnel resources, are known and accepted by the management. Quality Assurance should be involved in the approval of protocols and reports.

4.4.3. A Final Validation Report should be prepared. The conclusions of this report should state if the cleaning process has been validated successfully. Limitations that apply to the use of the validated method should be defined (for example, the analytical limit at which cleanliness can be determined). The report should be approved by the Plant Management.

4.4.4. The cleaning process should be documented in an SOP.

4.4.5. Records should be kept of cleaning performed in such a way that the following information is readily available:

(a) the area or piece of equipment cleaned,

(b) the person who carried out the cleaning,

(c) when the cleaning was carried out,

(d) the SOP defining the cleaning process,

(e) the product which was previously processed on the equipment being cleaned.

4.4.6. The cleaning record should be signed by the operator who performed the cleaning and by the person responsible for Production and should be reviewed by Quality Assurance.

4.5. Personnel

4.5.1. Operators who perform cleaning routinely should be trained in the application of validated cleaning procedures. Training records should be available for all training carried out.

4.5.2. It is difficult to validate a manual, i.e. an inherently variable/cleaning procedure. Therefore, operators carrying out manual cleaning procedures should be supervised at regular intervals.

4.6. Equipment

4.6.1. The design of the equipment should be carefully examined. 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.

4.6.2. Dedicated equipment should be used for products which are difficult to remove (e.g. tarry or gummy residues in the bulk manufacturing), for equipment which is difficult to clean (e.g. bags for fluid bed dryers), or for products with a high safety risk (e.g. biologicals or products of high potency which may be difficult to detect below an acceptable limit).

4.7. Microbiological Aspects

4.7.1. The existence of conditions favourable to reproduction of micro organisms (e.g. moisture, temperature, crevices and rough surfaces) and the time of storage should be considered. The aim should be to prevent excessive microbial contamination.

4.7.2. The period and when appropriate, the conditions of storage of equipment before and after cleaning and the time between cleaning and equipment

reuse, should form part of the validation of cleaning procedures. This is to provide confidence that routine cleaning and storage of equipment does not allow microbial proliferation.

4.7.3. In general, equipment should be stored dry, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations.

4.8. Sampling

4.8.1. Samples should be drawn according to the Cleaning Validation Protocol.

4.8.2. There are two methods of sampling that are considered to be acceptable, direct surface sampling (swab method) and indirect sampling (use of rinse solutions). A combination of the two methods is generally the most desirable, particularly in circumstances where accessibility of equipment parts can mitigate against direct surface sampling.

a. Direct Surface Sampling

The suitability of the material to be used for sampling and of the sampling medium should be determined. The ability to recover samples accurately may be affected by the choice of sampling material. It is important to ensure that the sampling medium and solvent are satisfactory and can be readily used.

b. Rinse Samples

Rinse samples allow sampling of a large surface area. In addition, inaccessible areas of equipment that cannot be routinely disassembled can be evaluated. However, consideration should be given to the solubility of the contaminant and the appropriate volume of the samples.

A direct measurement of the product residue or contaminant in the relevant solvent should be made when rinse samples are used to validate the cleaning process.

4.9. Detergents

4.9.1. The efficiency of cleaning procedures for the removal of detergent residues should be evaluated. Acceptable limits should be defined for levels of detergent after cleaning. Ideally, there should be no residues detected. The possibility of detergent breakdown should be considered when validating cleaning procedures.

4.9.2. The composition of detergents should be known to the manufacturer. If such information is not available, alternative detergents should be selected whose composition can be defined. As a guide, food

regulations may be consulted. The manufacturer should ensure, either by a written commitment or by a contract, that he is notified by the detergent supplier of any critical changes in the formulation of the detergent.

4.10. Analytical Methods

4.10.1. The analytical methods should be validated before the Cleaning Validation Study is carried out.

4.10.2. The analytical methods used to detect residuals or contaminants should be specific for the substance to be assayed and provide a sensitivity that reflects the level of cleanliness determined to be acceptable by the company.

4.10.3. The analytical methods should be challenged in combination with the sampling methods used, to show that the contaminants can be recovered from the equipment surface 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. A negative result may also be the result of poor sampling techniques.

4.11. Establishment of Limits

4.11.1. The pharmaceutical company's rationale for selecting limits for product residues should be logically based on a consideration of the materials involved and their therapeutic dose. The limits should be practical, achievable and verifiable.

4.11.2. The approach for setting limits can be:

(a) product specific Cleaning Validation for all products,

(b) grouping into product families and choosing a "worst case" product,

(c) grouping into groups of risk (e.g. very soluble products, similar potency, highly toxic products, difficult to detect).

4.11.3. Carry-over of product residues should meet defined criteria, for example the most stringent of the following criteria:

(a) no more than 0.1% of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product,

(b) no more than 10 ppm of any product will appear in another product,

(c) no quantity of residue should be visible on the equipment after cleaning procedures are performed. Spiking studies should determine the concentration at which most active ingredients are visible,

(d) for certain allergenic ingredients, penicillins, cephalosporins or potent steroids and cytotoxics, the limit should be below the limit of detection by best available analytical methods. In practice this may mean that dedicated plants are used for these products.

4.11.4. One cannot ensure that the contaminate will be uniformly distributed throughout the system. It is also an invalid conclusion to make the assumption that a residual contaminant would be worn off the equipment surface uniformly or that the contamination might only occur at the beginning of the batch.

4.11.5. In establishing residual limits, it may not be adequate to focus only on the principal reactant since chemical variations (active decomposition materials) may be more difficult to remove.

GLOSSARY

Definitions of terms relating to qualification and validation which are not given in the glossary of the current EC Guide to GMP, but which are used in this Annex, are given below.

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.

Change Management

A less formal approach to change control that is generally utilised during the preliminary planning and design stage of a project. (Many companies will elect to move straight to a change control system in a design stage of a complex project. This has the advantage of formality, more accurate records and documentation as well as a strong traceability and accountability feature).

Commissioning

An engineering term that covers all aspects of bringing a system or sub-system to a position where it is regarded as being ready for use in pharmaceutical manufacture. Commissioning involves all the basis requirements of Installation Qualification (IQ) and Operational Qualification (OQ).

Concurrent Validation

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

Critical Variable Study

A study that serves to measure variables (parameters) critical to the satisfactory operation of a piece of equipment or plant and to assure their operation within monitored and controlled limits. Examples of variables would be pressure, temperature, flow rates, time etc.

Design qualification (DQ)

The documented verification of the user requirements for an equipment and its ancillary systems.

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.

Limit of Detection

The lowest amount of analyte in a sample which can be detected 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 with defined precision and accuracy under the stated experimental conditions.

Minor changes

Changes having no direct impact on final or in-process product quality.

Operational Qualification (OQ)

Documented verification that the system or sub-system performs as intended throughout all anticipated operating ranges.

Process Validation

Documented verification that the integrated system functions as intended, in its normal operating environment. (The term Performance Qualification may be used also).

Note: Processes may be proven also by documented verification through appropriate testing that the finished product produced by a specified process meets all release requirements. This may be called Product Qualification.

Piping & Instrument Diagrams (P&IDs)

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

Pre-Determined Acceptance Criteria

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

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)

A process capability index CpK represents the true measure of process capability

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

or

$$\frac{USL - X}{3s}$$

where

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

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 equipment attributes related to the performance of a particular function or functions and allocation of certain limits or restrictions to those attributes.

Retrospective Validation

Validation of a process for a product which has been marketed based upon accumulated manufacturing, testing and control batch data.

Re-Validation

A repeat of the process validation to provide an 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.

Validation Master Plan

A document providing information on the company's 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 standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

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EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL
Industrial affairs III: Consumer goods industries
Pharmaceuticals and cosmetics

Brussels, 30 October 1999
E-3 D(99)

To Consultation Partners

Subject : **Validation master plan design qualification, installation and operational qualification, non-sterile process validation cleaning validation**

Dear Colleague,

The attached document is a draft annex to the 1997 EU Guide to Good Manufacturing Practice – Eudralex Volume 4.

It has been drafted in consultation with Member States Inspectors within the Expert Group on Inspections and Control of Medicinal Products.

I would appreciate receiving your comments by 28 February 2000.

Yours sincerely,

Ph. Brunet
Acting Head of Unit

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