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Health Products and Food Branch Inspectorate

Validation Guidelines for Pharmaceutical Dosage Forms

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Ce document est aussi disponible en français.

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1.0 Scope

This Guidance document has been prepared to provide guidance to the pharmaceutical industry in dealing with validation issues for sterile and non-sterile dosage forms, biologicals, and radiopharmaceuticals. It should be noted that additional guidance related to sterile products and not contained in this document should also be considered. These requirements may be found in supplemental process validation guidelines available on the Inspectorate's website. (<http://www.hc-sc.gc.ca/dhp-mps/compli-conform/index-eng.php>)

It is expected that importers and distributors of drug products have documented evidence that their vendors meet validation requirements.

2.0 Introduction

This document provides guidance on issues and topics related to systems, equipment qualification, product and process validation for sterile and non-sterile dosage forms. These topics reflect an area in pharmaceutical, biological, and, radiopharmaceuticals manufacture that is noted as being important by both the Inspectorate and the pharmaceutical industry. These guidelines have been prepared to provide guidance to inspectors, evaluators and the industry in dealing with issues related to validation. Utilization of this information should facilitate compliance with Division 2, Part C of the *Regulations to the Food and Drugs Act*.

It is not intended that the recommendations made in these guidelines become requirements under all circumstances. Information provided in the Interpretation section for limits to be applied in defined circumstances, as well as the number of batches to be utilized for validation studies are for guidance purposes only. Inspectors, evaluators and the industry may consider other alternate means if proposed and documented with appropriate scientific justification.

3.0 Purpose

These guidelines outline the general principles that the Inspectorate considers to be acceptable elements of validation which may be used by fabricators, packagers/labellers for drug products. The Guidelines on Good Manufacturing Practices (GMP), Division 2, Part C of the Food and Drug Regulations require that:

- all critical production processes be validated
- validation studies are conducted in accordance with pre-defined protocols. Written reports summarizing recorded results and conclusions are prepared, evaluated, approved and maintained
- changes to production processes, operating parameters, equipment or materials that may affect product quality and/or the reproducibility of the process are also to be validated prior to implementation.

These guidelines are not intended to specify how validation is to be conducted, but are indicators of what is expected to be covered by fabricators, packagers/labellers.

The elements of validation presented in these guidelines are not intended to be all-encompassing. The particular requirements of validation may vary according to factors such as the nature of drug products eg. sterile, non-sterile, biologicals, and the complexity of the process. The concepts provided in these guidelines have general applicability and provide an acceptable framework for establishing a comprehensive approach to validation.

4.0 Definitions

Change Control (contrôle des changements): A written procedure that describes the action to be taken if a change is proposed (a) to facilities, materials, equipment, and/or processes used in the fabrication, packaging, and testing of drugs, or (b) that may affect the operation of the quality or support system.

Cleaning Validation (validation des procédés de nettoyage): The documented act of demonstrating that cleaning procedures for the equipment used in fabricating/packaging will reduce to an acceptable level all residues (products/cleaning agents) and to demonstrate that routine cleaning and storage of equipment does not allow microbial proliferation.

Concurrent Validation (validation concomitante): A process where current production batches are used to monitor processing parameters. It gives assurance of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch.

Critical Process Parameter (paramètre critique du procédé): A parameter which if not controlled will contribute to the variability of the end product.

Equipment Qualification (qualification de l'équipement): Studies which establish with confidence that the process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. The studies must include equipment specifications, installation qualification (IQ), and operational qualification (OQ) of all major equipment to be used in the manufacture of commercial scale batches. Equipment Qualification should simulate actual production conditions, including "worst case"/ stressed conditions.

Installation Qualification (qualification d'installation): The documented act of demonstrating that process equipment and ancillary systems are appropriately selected and correctly installed.

Major Equipment (équipement principal): A piece of equipment which performs significant processing steps in the sequence of operations required for fabrication/packaging of drug products. Some examples of major equipment include tablet compression machines, mills, blenders, fluid bed dryers, heaters, drying ovens, tablet coaters, encapsulators, fermentors, centrifuges, etc.

Master Production Document (document-type de production): A document that includes specifications for raw material, for packaging material and for packaged dosage form, master formula, sampling procedures, and critical processing related standard operating procedures (SOPs), whether or not these SOPs are specifically referenced in the master formula.

Measuring Devices (instruments de mesure): A device used in monitoring or measuring process parameters.

Operational Qualification (qualification opérationnelle): The documented action of demonstrating that process equipment and ancillary systems work correctly and operate consistently in accordance with established specifications.

Process Capability (capacité du procédé): Studies conducted to identify the critical process parameters that yield a resultant quality, and their acceptable specification ranges, based on the established +/- 3 sigma deviations of the process, under stressed conditions but when free of any assignable causes.

Process Qualification (qualification du procédé): The phase of validation dealing with sampling and testing at various stages of the manufacturing process to ensure that product specifications are met.

Process Re-validation (revalidation du procédé): Required when there is a change in any of the critical process parameters, formulation, primary packaging components, raw material fabricators, major equipment or premises. Failure to meet product and process specifications in sequential batches would also require process re-validation.

Process Validation (validation du procédé): Establishing documented evidence with a high degree of assurance, that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. Process validation may take the form of Prospective, Concurrent or Retrospective Validation and Process Qualification or Re-validation.

Prospective Validation (validation prospective): Conducted prior to the distribution of either a new product or a product made under a modified production process, where the modifications are significant and may affect the product's characteristics. It is a pre-planned scientific approach and includes the initial stages of formulation development, process development, setting of process specifications, developing in-process tests, sampling plans, designing of batch records, defining raw material specifications, completion of pilot runs, transfer of technology from scale-up batches to commercial size batches, listing major process equipment and environmental controls.

Retrospective Validation (validation rétrospective): Conducted for a product already being marketed, and is based on extensive data accumulated over several lots and over time. Retrospective Validation may be used for older products which were not validated by the fabricator at the time that they were first marketed, and which are now to be validated to conform to the requirements of Division 2, Part C of the Regulations to the Food and Drugs Act.

Validation (validation): The documented act of demonstrating that any procedure, process, and activity will consistently lead to the expected results. Includes the qualification of systems and equipment.

Validation Master Plan (plan maître de validation): An approved written plan of objectives and actions stating how and when a company will achieve compliance with the GMP requirements regarding validation.

Validation Protocol (protocole de validation): A written plan of actions stating how process validation will be conducted; it will specify who will conduct the various tasks and define testing parameters; sampling plans, testing methods and specifications; will specify product characteristics, and equipment to be used. It must specify the minimum number of batches to be used for validation studies; it must specify the acceptance criteria and who will sign/approve/ disapprove the conclusions derived from such a scientific study.

Validation Team (équipe de validation): A multi-disciplinary team of personnel primarily responsible for conducting and/or supervising validation studies. Such studies may be conducted by person(s) qualified by training and experience in a relevant discipline.

Worst Case Condition (condition de la pire éventualité): The highest and /or lowest value of a given parameter actually evaluated in the validation exercise.

5.0 Phases of Validation

The activities relating to validation studies may be classified into three phases:

Phase 1:

Pre-Validation Phase or the Qualification Phase, which covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, Equipment Qualification, Installation Qualification, master production documents, Operational Qualification, Process Capability.

Phase 2:

Process Validation Phase (Process Qualification phase) designed to verify that all established limits of the Critical Process Parameters are valid and that satisfactory products can be produced even under the “worst case” conditions.

Phase 3:

Validation Maintenance Phase requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including Change Control procedures.

At this stage the Validation Team also assures that there have been no changes/ deviations that should have resulted in Requalification and Revalidation.

6.0 Interpretation

General Concepts:

Quality, safety and effectiveness must be built into the product. This requires careful attention to a number of factors such as the selection of quality materials/components, product and process design, control of processes, in-process control, and end-product testing.

Due to the complexity of the drug products, routine end-product testing alone is not sufficient due to several reasons. Furthermore, quality cannot be tested into the finished drug product but rather be built in the manufacturing processes and these processes should be controlled in order that the finished product meets all quality specifications. A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications.

Validation protocol:

A written plan stating how validation will be conducted, including test parameters, product characteristics, production and packaging equipment, and decision points on what constitutes acceptable test results. This document should give details of critical steps of the manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be tested.

The validation protocol provides a synopsis of what is hoped to be accomplished. The protocol should list the selected process and control parameters, state the number of batches to be included in the study, and specify how the data, once assembled, will be treated for relevance. The date of approval by the validation team should also be noted.

In the case where a protocol is altered or modified after its approval, appropriate reasoning for such a change must be documented.

The validation protocol should be numbered, signed and dated, and should contain as a minimum the following information:

- objectives, scope of coverage of the validation study
- validation team membership, their qualifications and responsibilities
- type of validation: prospective, concurrent, retrospective, re-validation
- number and selection of batches to be on the validation study
- a list of all equipment to be used; their normal and worst case operating parameters
- outcome of IQ, OQ for critical equipment
- requirements for calibration of all measuring devices
- critical process parameters and their respective tolerances
- description of the processing steps: copy of the master documents for the product
- sampling points, stages of sampling, methods of sampling, sampling plans
- statistical tools to be used in the analysis of data
- training requirements for the processing operators
- validated test methods to be used in in-process testing and for the finished product
- specifications for raw and packaging materials and test methods
- forms and charts to be used for documenting results
- format for presentation of results, documenting conclusions and for approval of study results.

Validation Master Plan:

A validation master plan is a document that summarises the company's overall philosophy, intentions and approaches to be used for establishing performance adequacy. The Validation Master Plan should be agreed upon by management.

Validation in general requires meticulous preparation and careful planning of the various steps in the process. In addition, all work should be carried out in a structured way according to formally authorised standard operating procedures. All observations must be documented and where possible must be recorded as actual numerical results.

The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements of it being the list/inventory of the items to be validated and the planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as well as re-validation.

The Validation Master Plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's and validation protocols and reports

The format and content should include:

- introduction: validation policy, scope, location and schedule
- organizational structure: personnel responsibilities

- plant/process/product description: rational for inclusions or exclusions and extent of validation
- specific process considerations that are critical and those requiring extra attention
- list of products/ processes/ systems to be validated, summarized in a matrix format, validation approach
- re-validation activities, actual status and future planning
- key acceptance criteria
- documentation format
- reference to the required SOP's
- time plans of each validation project and sub-project.

Installation and Operational Qualification:

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. Installation and Operational Qualification exercises assure through appropriate performance tests and related documentation that equipment, ancillary systems and sub-systems have been commissioned correctly. The end results are that all future operations will be reliable and within prescribed operating limits.

The basic principles are:

- equipment be correctly installed in accordance with an installation plan
- requirements for calibration, maintenance and cleaning be covered in approved SOP's
- tests be conducted to assure that equipment is operating correctly, under normal and "worst case" conditions
- operator training requirements pertaining to new equipment be conducted and documented.

At various stages in a validation exercise there is need for protocols, documentation, procedures, equipment, specifications and acceptance criteria for test results. All these need to be reviewed, checked and authorised. It would be expected that representatives from the appropriate professional disciplines, eg. Engineering , Research and Development, Manufacturing, Quality Control and Quality Assurance be actively involved in these undertakings with the final authorisation given by a validation team or the Quality Assurance representative.

Installation Qualification (IQ):

IQ is the method of establishing with confidence that all major processing, packaging equipment and ancillary systems are in conformance with installation specifications, equipment manuals, schematics and engineering drawings. This stage of validation includes examination of equipment design, determination of calibration, maintenance and adjustment requirements.

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 IQ stage, thus leading to a reduction in the scope of the IQ checks.

All equipment, gauges and services should be adequately identified and should be given a serial number or other reference number. This number should appear in the reports for the equipment validation studies conducted.

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. These checks, tests and challenges should be repeated a significant number of times to assure reliable and meaningful results.

At the IQ stage the company should document preventive maintenance requirements for installed equipment. The preventive maintenance schedule should be incorporated into the routine maintenance schedule.

Note:

There will be cases where installation of the equipment had not been qualified at the time of installation, and the engineering drawings and manuals for the equipment are no longer available at the manufacturing site. However, the equipment in place operates for a lengthy period of time without any problem or modifications of its design since it was first installed. In such situations, the Inspectorate considers that it may be appropriate for those specific cases to verify a limited number of the most critical parameters demonstrating that the equipment had been adequately installed. Thereafter, the company could pass directly to the operational qualification (OQ) stage if there is sufficient documented evidence that these units have always been well maintained and calibrated according to an adequate pre-established schedule.

Operational Qualification (OQ):

The conduct of an Operational Qualification should follow an authorised protocol. The critical operating parameters for the equipment and systems should be identified at the OQ stage. The plans for the OQ 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 include a condition or a set of conditions encompassing upper and lower processing and operating limits referred to as "worst-case" conditions. The completion of a successful OQ 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.

The completion of satisfactory IQ and OQ exercises should permit a formal "release" of the equipment for the next stage in the process validation exercise as long as calibration, cleaning, preventive maintenance and operator training requirements have been finalised and documented.

Re-Qualification:

Modifications to, or relocation of equipment should follow satisfactory review and authorization of the documented change proposal through the change control procedure. This formal review should include consideration of re-qualification of the equipment. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system of the preventative maintenance program.

Process Validation:

It would normally be expected that process validation be completed prior to the distribution of a 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 without any significant changes may also be validated according to an approved protocol (Retrospective Validation).

a) Prospective Validation:

In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase 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 parameters that may affect the quality of the finished product. A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorised protocol.

All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents 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.

Using this defined process a series of batches 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 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 these data.

Some considerations should be exercised when selecting the process validation strategy. Amongst these should be the use of different lots of active raw materials and major excipients, batches produced on different shifts, the use of different equipment and facilities dedicated for commercial production, operating range of the critical processes, and a thorough analysis of the process data in case of Requalification and Revalidation.

During the processing of the validation batches, extensive sampling and testing should be performed on the product at various stages, and should be documented comprehensively. Detailed testing should also be done on the final product in its package.

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 Batch manufacturing and packaging record or into appropriate standard operating procedures. Limits, frequencies and actions to be taken in the event of the limits being exceeded should be specified.

Matrix or “Family” approaches to prospective process validation:

It may be possible and acceptable in particular circumstances for a manufacturer that uses the same process for several related products to develop a scientifically sound validation plan for that process rather than different plans for each product manufactured by that process.

The matrix approach generally means a plan to conduct process validation on different strengths of the same product. However, discrete manufacturing steps such as compression, and coating that involve different tools, equipment, and process conditions for the different dosage strengths can not be generally validated using the matrix approach. It should be recognized that the matrix approach has limitations when there are concerns with respect to physical characteristics such as flow properties, particle size distribution, homogeneity.

The “family” approach means a plan to conduct process validation on different products manufactured with the same processes using the same equipment.

The validation process using these approaches must include batches of different strengths or products which should be selected to represent the worst case conditions or scenarios to demonstrate that the process is consistent for all strengths or products involved.

b) Concurrent Validation:

Unconditional use of this approach is not encouraged by the Inspectorate and is not acceptable as being the “norm”. In using this approach there is always the risk of having to modify process parameters or specifications over a period of time. This situation often leads to questions regarding disposition of the batches that had already been released for sale, subsequently known to have undesired quality characteristics.

Concurrent validation may be the practical approach under certain circumstances. Examples of these may be:

- when a previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site
- where the product is a different strength of a previously validated product with the same ratio of active / inactive ingredients
- when the number of lots evaluated under the Retrospective Validation were not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control
- when the number of batches produced are limited (e.g. orphan drugs).

It is important in these cases however, that the systems and equipment to be used have been fully validated previously. The justification for conducting concurrent validation must be documented and the protocol must be approved by the Validation Team. A report should be prepared and approved prior to the sale of each batch and a final report should be prepared and approved after the completion of all concurrent batches. It is generally considered acceptable that a minimum of three consecutive batches within the finally agreed parameters, giving the product the desired quality would constitute a proper validation of the process.

c) Retrospective Validation:

In many establishments, processes that are stable and in routine use have not undergone a formally documented validation process. Historical data may be utilized to provide necessary documentary evidence that the processes are validated.

The steps involved in this type of validation still require the preparation of a protocol, the reporting of the results of the data review, leading to a conclusion and recommendation.

Retrospective validation is only acceptable for well established detailed processes that include operational limits for each critical step of the process and will be inappropriate where there have been recent changes in the formulation of the product, operating procedures, equipment and facility.

The source of data for retrospective validation should include amongst others, batch documents, process control charts, annual product quality review reports, maintenance log books, process capability studies, finished product test results, including trend analyses, and stability results.

For the purpose of retrospective validation studies, it is considered acceptable that data from a minimum of ten consecutive batches produced be utilized. When less than ten batches are available, it is considered that the data are not sufficient to demonstrate retrospectively that the process is fully under control. In such cases the study should be supplemented with data generated with concurrent or prospective validation.

Some of the essential elements for Retrospective Validation are:

- Batches manufactured for a defined period (minimum of 10 last consecutive batches)
- Number of lots released per year
- Batch size/strength/manufacturer/year/period
- Master manufacturing/packaging documents
- Current specifications for active materials/finished products
- List of process deviations, corrective actions and changes to manufacturing documents
- Data for stability testing for several batches
- Trend analyses including those for quality related complaints

Process Re-Validation:

Re-validation provides the evidence that changes in a process and /or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process.

Periodic review and trend analysis should be carried out at scheduled intervals. Re-validation becomes necessary in certain situations. The following are examples of some of the planned or unplanned changes that may require re-validation:

- Changes in raw materials (physical properties such as density, viscosity, particle size distribution, and moisture, etc., that may affect the process or product).
- Changes in the source of active raw material manufacturer
- Changes in packaging material (primary container/closure system).
- Changes in the process (e.g., mixing time, drying temperatures and batch size)
- Changes in the equipment (e.g. addition of automatic detection system). Changes of equipment which involve the replacement of equipment on a “like for like” basis would not normally require a re-validation except that this new equipment must be qualified.
- Changes in the plant/facility.
- Variations revealed by trend analysis (e.g. process drifts)

A decision not to perform re-validation studies must be fully justified and documented.

Change Control:

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, processing site, method of production or testing or any other change that may affect product quality or support system operations.

All changes must be formally requested, documented and accepted by the Validation Team. The likely impact /risk of the change on the product must be assessed and the need for the extent of re-validation should be determined.

Commitment of the company to control all changes to premises, supporting utilities, systems, materials, equipment and processes used in the fabrication/packaging of pharmaceutical dosage forms is essential to ensure a continued validation status of the systems concerned.

The change control system should ensure that all notified or requested changes are satisfactorily investigated, documented and authorised. Products made by processes subjected to changes should not be released for sale without full awareness and consideration of the change by the Validation Team. The Team should decide if a re-validation must be conducted prior to implementing the proposed change.

7.0 References

1. Guidelines on General Principles of Process Validation, CDER, US-FDA 1987
2. Pharmaceutical Process Validation; 2nd edition, Editors: I. R. Berry and R.A. Nash, 1993
3. Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation, PIC/S September, 2007.