# Guide to validation – drugs and supporting activities

## GUI-0029

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Canada

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The following are the three types of icons used in this document, and the way they are intended to be used.

**Important:** Key or cautionary information for people to know.

**Information:** Supplementary information like quotes and legal references.

**Tip:** Things to do or understand.

# About this document

## 1. Purpose

This document is for anyone involved in the fabrication, packaging/labelling, testing, importation, distribution and wholesaling of drugs.

It describes how to properly qualify and validate drug manufacturing processes, facilities, equipment, utilities and analytical methods. The application of this document will vary depending on the nature of your operations.

This document will help you to comply with Part C, Division 2 of the Food and Drug Regulations, (the Regulations).

It has been revised with a view to harmonize with current guidance from other regulatory agencies and organizations such as the United States Food and Drug Administration (US FDA), European Medicines Agency (EMA), Pharmaceutical Inspection Cooperation Scheme (PIC/S), International Council for Harmonisation (ICH) and World Health Organization (WHO).

## 2. Scope

These guidelines apply to the following types of drugs:

- pharmaceutical
- radiopharmaceutical
- biological
- veterinary

This document outlines general validation requirements. Information for more specific topics (e.g. sterile products) can be found in these Health Canada guidelines:

- *Process Validation: Gaseous Sterilization for Pharmaceuticals (GUI-0007)*
- *Process Validation: Irradiation Sterilization for Pharmaceuticals (GUI-0009)*
- *Process Validation: Moist Heat Sterilization for Pharmaceuticals (GUI-0010)*

Additional guidance on validation related activities for certain lower risk veterinary drugs and Category IV monograph drugs can be found in these guidance documents;

- *Guidance Document Annex 4 to the Current Edition of the Good Manufacturing Practices Guidelines - Veterinary Drugs (GUI-0012)*
- *Annex 7 to Good manufacturing practices guide for drug products - Selected non-prescription drugs (GUI-0066)*

Importers and distributors of drug products must have documented evidence that their vendors meet these validation requirements. Refer to *Good manufacturing practices guide for drug products (GUI-0001)* (Records section), for additional information.

Health Canada has adopted the Guideline *ICH Q7A: Good Manufacturing Practice for Active Pharmaceutical Ingredients*. This document may be used as supplementary optional guidance for validation activities for active pharmaceutical ingredients (APIs).

# 3. Introduction

These guidelines interpret the requirements for good manufacturing practices (GMP) in Part C, Division 2 of the Regulations. They were developed by Health Canada in consultation with stakeholders.

Guidance documents like this one are meant to help industry and health care professionals understand how to comply with regulations. They also provide guidance to Health Canada staff, so that the rules are enforced in a fair, consistent and effective way across Canada.

Health Canada inspects establishments to assess their compliance with the *Food and Drugs Act* (the Act) and associated regulations. When we conduct an inspection, we will use this document as a guide in assessing your compliance with GMP requirements.

These guidelines are not the only way GMP regulations can be interpreted, and are not intended to cover every possible case. Other ways of complying with GMP regulations will be considered with proper scientific justification. Also, as new technologies emerge, different approaches may be called for.

Guidance documents are administrative and do not have the force of law. Because of this, they allow for flexibility in approach. Use this guide to help you develop specific approaches that meet your unique needs.

# Guidance

## 4. Principles

An effective process validation program is critical in ensuring that manufacturing processes will consistently produce acceptable product and are appropriately controlled. Such a program would ensure that:

- manufacturing processes are well understood
- control strategies are implemented to account for all identified sources of variability
- each step of the manufacturing process is sufficiently controlled to ensure that finished product consistently meets requirements

**Process validation** – The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products. *Process Validation: General Principles and Practices, US FDA.*

Validation is not a single study—it represents the cumulative knowledge gained during product development and manufacture. Process validation should incorporate a lifecycle approach, including:

- product and process development
- qualification of the commercial manufacturing process
- maintenance of the process in a state of control during routine commercial production

**Qualification** – Activities undertaken to demonstrate that facilities, utilities, equipment and processes are suitable for their intended use.

Ensure you apply quality risk management (QRM) principles when developing your validation program and individual validation studies. Use these principles to determine the scope and extent of study requirements. Document and justify all decisions made.

You may wish to consider the following ICH guidance documents for additional information as you develop your approach to process validation:

- *ICH Q7: Good Manufacturing Practice for Active Pharmaceutical Ingredients*
- *ICH Q8 (R2): Pharmaceutical Development*
- *ICH Q9: Quality Risk Management*
- *ICH Q10: Pharmaceutical Quality System*
- *ICH Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)*

# 5. General validation requirements

1. Prepare a Validation Master Plan or equivalent document that includes the following:
    a. a summary of validation and qualification policies, requirements and strategies including how life cycle and QRM concepts are being applied
    b. the organization structure related to validation requirements (including an adequate description of roles and responsibilities)
    c. a summary of the facilities, equipment, analytical methods, systems and processes on site and their associated qualification/validation status
    d. guidance with respect to the development of acceptance criteria
    e. a summary of change control and deviation policies for qualification and validation
    f. a summary of measures to be taken to ensure processes remain in a state of control

Additional general guidance on validation and validation master plans can be found in the following PIC/S documents:

- *PIC/S GMP Guide - Annex 15 - Qualification and Validation* (PE 009-14)
- *PIC/S - Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation* (PI 006-3)

2. For large and complex projects you may want to generate a project specific Validation Master Plan to ensure:
    - such projects are appropriately planned and controlled
    - the inter-relationship between various documents and studies for such projects is clearly defined

3. Define reporting requirements in the quality system. Qualification and validation personnel do not necessarily need to report to quality management. The key consideration is that there is quality oversight throughout the validation life cycle and appropriate approval or authorization to progress to the next stage in a qualification or verification study.

4. Ensure personnel performing qualification and validation studies are trained and qualified when needed, and that they follow procedures.

5. Ensure all documents generated during qualification and validation are approved and authorized by appropriate personnel and by the quality department.

6. It is important that documents or data provided by third parties are approved by designated personnel (including quality) at your company. Vendor supplied protocols may need to be supplemented with additional documentation.

7. Apply good documentation practices throughout the product lifecycle.

8. Record any failure to meet predefined acceptance criteria as a deviation within your quality system. Any implications to validation studies should be discussed in the final report.

9. Any significant changes to the protocol during execution will need to be fully explained and justified. Such changes should be handled in accordance with a company's quality management system.

10. Incorporate checks into qualification and validation work, in order to ensure the integrity of data obtained.

# 6. Lifecycle approach to process validation

The success of your validation program depends on properly executing each phase within the product's lifecycle:

- Phase 1 – Process design
- Phase 2 – Process performance qualification
- Phase 3 – Ongoing process verification

## 6.1 Phase 1 – Process design

1. This phase involves developing and optimizing a manufacturing process that consistently produces product meeting the required Quality Target Product Profile (QTPP).

**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.

**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.

**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.

Definitions are from ICH Q8(R2): Pharmaceutical Development

2. The QTPP is normally defined at the beginning of Phase 1 as it represents the objective of the development process. It should be referenced throughout the product lifecycle and may need to be revisited as product and process understanding improve.

3. To meet this objective:

   a. Ensure you understand the manufacturing process thoroughly, including potential sources of variability and the impact of that variability on the product's critical quality attributes (CQA). Regularly conduct documented risk assessments to help develop this understanding as process/product knowledge is gained.

   b. Establish an adequately defined manufacturing process with suitable control strategies to account for identified sources of variability. Control strategies, should be applied in a way that is relative to the level of risk associated with the source(s) of variability. "In other words, a higher degree of control is appropriate for attributes or parameters that pose a higher risk." (US FDA Guidance for Industry, *Process Validation: General Principles and Practices*). The control strategy should be science based and holistic in nature. Appropriate controls and monitoring need to be established for raw materials, all processing steps, critical process parameters and critical quality attributes. Control strategies should also be regularly re-evaluated. The identification of critical process parameters (CPP) and the implementation of controls during Phase 1 is an important element of both pre-market submissions and ensuring an adequately controlled process.

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 on monitoring and control. (Reference ICH Q10: *Pharmaceutical Quality System*)

You may only establish adequate control strategies if the underlying manufacturing process is suitable. Discuss your manufacturing process choice in your pre-market submission to Health Canada.

Examples of sources of variation and potential control strategies are provided in Table 1.

Table 1 – Examples of potential control strategies for sources of variation

| Potential source of variation | Potential control strategy |
|---|---|
| Product sensitive to temperature, moisture or light | • Optimizing the formulation or manufacturing process to reduce the effects of environmental factors.<br>• Tightening environmental controls for temperature, humidity and/or light.<br>• Designing packaging in a manner that provides product protection. |
| Inconsistent periods of time between manufacturing steps (hold time) | • Establishing allowable hold times based on scientific evaluation and experimental data for in-process and bulk material.<br>• Allowable product hold times should be assessed following a risk based approach by evaluating available data with respect to immediate and long-term impact (i.e. over the shelf life of the product). In general, it is expected that studies are conducted that are representative of the commercial process (e.g. |

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| | equivalent formulation, process, storage vessels, conditions, etc…).<br><br>Note: Microbial growth and endotoxins may be a consideration in determining allowable hold times for some products.<br><br>Additional guidance on hold time studies can be found in the following documents.<br><br>• *Health Canada Guidance Document: Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)*<br><br>• *ICH Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological Biological Products*<br><br>• *WHO Annex 4-TRS992: General Guidance on Hold Time Studies* |
| Adjustable manufacturing and equipment parameters | • Implementing manufacturing parameters based on data driven scientific evaluation and experimentation.<br><br>Note: You do not need to test until the edge of failure, but data should be available to verify that manufacturing parameter ranges produce results meeting specifications. Identify and justify critical process parameters as part of your pre-market submission to Health Canada. Avoid manual processes that cannot be validated in a meaningful manner such as the use of bags to hand mix APIs and excipients. |
| Raw material variability | • Implementing appropriate controls which can include a vendor selection/certification program and enhanced material specifications. There may be a requirement to have material specifications that go beyond compendial requirements. |

4. To reduce overall variability, you may use process analytical technology (PAT) as a control strategy to measure and control variables.

5. Knowledge management or transfer is a key component of the successful implementation of a lifecycle approach to validation. It is important that you document and justify conclusions about sources of variability, the impact of the variability, and the associated control strategies.

6. Development studies are often conducted on laboratory or pilot-scale batches. It is important to ensure that appropriate scale-up studies are conducted. Identifying parameters potentially impacted by scale is an important consideration in the development phase. See *Health Canada Guidance Document – Quality (Chemistry and Manufacturing Guidance: New Drug Submission (NDSs) and Abbreviated New Drug Submissions (ANDSs)* for more guidance on the relative size of pilot scale batches.

Health Canada expects that a significant part of the information and knowledge you learn during the process design phase becomes part of your pre-market submission.

## 6.2 Phase 2 – Process performance qualification (PPQ)

Phase 2 involves confirming that the commercial-scale manufacturing process:

- functions in a state of control
- consistently produces product meeting its critical quality attributes

Starting the PPQ study represents the end of development and beginning of commercial manufacture.

1. Conduct a readiness assessment to verify that you are ready to start PPQ batch manufacture. Items to verify in a readiness assessment include the following:
    - adequate manufacturing understanding/controls have been established from the process design phase
    - manufacturing instructions are sufficiently detailed to ensure batches are manufactured in a reproducible manner

- facility, equipment and systems are ready for commercial batch manufacture (refer to sections 8.1 Facility, equipment and utility qualification and 8.3 Computer System Validation)
- analytical methods have been validated (refer to section 8.2 Analytical Method Validation)
- all manufacturing and validation personnel are adequately trained

2. Manufacture PPQ batches at commercial scale, according to GMP requirements and the manufacturing process/parameter ranges established during Phase 1.

3. Consider whether qualification batches should be enrolled into the ongoing stability program. This will depend on the extent of stability monitoring conducted during the design phase and the extent of process variability (such as maximum hold times, different raw material suppliers or lots) incorporated into the qualification batches.

### 6.2.1 Protocol

Conduct all PPQ studies according to a preapproved protocol. This protocol document should include:

- a brief description of the process with reference to the master batch record, and other relevant supporting documents
- validation team membership including roles and responsibilities
- summaries of CQAs to be investigated CPPs with associated limits and any other non-critical attributes and parameters which will be monitored
- intermediate and finished product sampling and testing requirements; sampling plans and acceptance criteria should be justified
- in-process testing controls and acceptance criteria
- proposed number of PPQ batches to be made (see section 6.2.2 Number of process qualification batches)
- a description of any challenge plans to be included (see section 6.2.3 Challenge plans)
- a summary of the evaluation of the site's readiness for the qualification study as described above

### 6.2.2 Number of process qualification batches

1. Determine the number of PPQ batches to evaluate using a documented risk assessment. Justify this decision within your qualification protocol. The decision should also be based on the protocol presented in pre-market submissions and the product and process knowledge gained about the product. Although a three-batch qualification effort has long been the industry norm, your risk assessment may result in a recommendation to evaluate a different number of batches.

   Items to consider in the risk assessment include:

   - overall process knowledge
     - Product transfer: The comparability of the equipment/manufacturing process and transfer of knowledge between sites are key considerations.
     - New products: Evaluate the extent of development and confidence in the studies.
   - experience with the process (including at commercial scale) and similar products
   - complexity of the process
   - potential process variation
   - equipment variability
   - inherent product risk (e.g. narrow therapeutic range, modified release drugs)

2. Based on the results of your risk assessment, a grouping strategy to the process qualification study may also be acceptable. For example, a bracketing approach might evaluate the extremes of a single variable, such as multiple strengths of a tablet using common granulation. Such a strategy could involve additional batches of the highest and lowest strength tablets and reduced evaluation of all intermediate strengths.

3. It is generally expected that you will conduct PPQ studies in a **prospective** manner. The studies should be completed, evaluated and deemed to be successful before commercial distribution of any batches.

   a. **Concurrent** validation may be acceptable in exceptional circumstances, for example, where there is a strong benefit–risk ratio for the patient. Concurrent validation may be considered appropriate when involving drugs for which there may be a limited demand (e.g. orphan drugs, or veterinary drugs with limited uses) and drugs with short expiry dates (e.g. radiopharmaceuticals, including positron emission tomography drugs). Concurrent validation may also be appropriate, in coordination with Health Canada, to alleviate shortages of medically necessary drugs.

b. Document and justify the decision to conduct the qualification study concurrently.

c. Summarize results in an interim report (or equivalent) to justify release of the lots.

4. It is expected that the lots for PPQ will be made consecutively.

"Consecutively" doesn't mean that the batches need to be immediately produced one after the other. It means that every lot to be made in support of the qualification be designated a qualification batch at the outset and executed as such. If there is intervening production of any drug on the same equipment where manufacturing issues related to quality are identified, these are reported and assessed in the validation.

### 6.2.3 Challenge plans

Manufacture qualification batches at commercial scale according to the approved manufacturing instructions under normal operating conditions. Worst-case process parameter challenges are not always practical or required during the process qualification stage. As such, it is important that actual manufacturing parameter ranges are based on sound scientific and experimental data (as determined during Phase 1- Process design).

It may be appropriate to challenge the parameters intended to be adjusted during normal production (e.g. tablet presses or filling machines for which operators may adjust speeds). The decision will depend on the extent of process knowledge gained during Phase 1, and whether all scalability concerns have been thoroughly addressed.

Other items to consider challenging during the process qualification study execution include the following (if practical and relevant).

- Different API and critical excipient lots. This can account for lot to lot differences. Note: APIs and critical excipients sourced from different vendors are a potential source of variability and may require additional evaluation and/or testing.
- Interchangeable equipment. Qualification studies may be used in demonstrating that the use of interchangeable equipment will not impact quality. In such cases, there should be documented justification as to why equipment may be considered interchangeable and why separate process qualification studies are not required.
- Different personnel. Attempts should be made to ensure that qualification batches are produced by different personnel and on different shifts.

- **Production interruptions.** Production interruptions, such as shift changes and periods of inactivity should be incorporated into the study.
- **Hold times and process durations.** Consideration should be given to evaluating potential impact of hold time and process durations if such factors were not adequately assessed during development.
- **Reprocessing.** This means subjecting all or part of the batch to a previous step in the process. Reprocessing should be validated. It is occasionally necessary and is generally pre-approved in the marketing authorization. Reprocessing is far more common in the manufacture of APIs than in finished dosage forms. (See definition in *Good manufacturing practices guide for drug products (GUI-0001)*)

### 6.2.4 Distinct manufacturing step requirements

Frequently, drugs are manufactured in a series of very different or distinct processing steps, sometimes referred to as unit operations. For example, an API process could include multiple reaction and purification steps. You must control each of these distinct manufacturing steps to ensure the overall manufacturing process is consistent and reproducible. Evaluate manufacturing steps by:

- ensuring that qualification batch critical process parameters and other manufacturing parameters meet batch record requirements
- evaluating manufacturing parameters and in-process data via statistical techniques, where applicable, to verify the unit operation is functioning in a state of control
- verifying that the manufacturing step produces the desired intermediate that meets predefined acceptance criteria. Testing should focus on parameters and attributes known to impact downstream process-ability/quality.

### 6.2.5 Sampling and testing plan requirements

1. Sampling and testing plans need to be designed to demonstrate consistency at intermediate stages as well as in the final filled product. For each stage of manufacture being assessed:

    - Sampling and testing plans should focus on the quality attributes most likely to demonstrate intra and inter batch variability.

- Sampling and testing plans and their associated acceptance criteria should be appropriately justified and statistically based, where required.

- Sampling locations should be chosen to include those that represent the highest potential for variability. This is of special concern for processes that produce unit dose products, such as tablets or capsules or those with the potential of material segregation or non-uniformity, such as filling suspensions into tubes.

- Sampling should be performed to provide an across the batch representation, that assesses the typical batch stages such as start up, shut down, shift changes, downtime, machine adjustments, hopper replenishments etc. If any challenge studies are incorporated, sampling should account for that challenge's effect on the process.

- Sampling and testing plans should be tailored to the type of material being produced at that stage. For example, if a unit manufacturing step is producing a true solution, sampling may be reduced compared to making a potentially less uniform powder or suspension mixture.

- Sampling methods and tools should be carefully selected to provide representative samples without affecting the homogeneity of the surrounding material.

2. Ensure your Process Performance Qualification (PPQ) protocol clearly outlines and justifies all sampling and testing requirements (including test methods).

### 6.2.6 Acceptance Criteria

The PPQ study acceptance criteria should demonstrate the manufacturing process is adequately controlled and produces consistent results. Elements for consideration as acceptance criteria include the following:

a. All process parameters are within the predefined normal operating ranges, particularly CPPs as defined in the control strategy.

b. Product quality attributes meet the pre-defined acceptance criteria and include statistical criteria where appropriate. Product quality testing should provide a high degree of assurance that batches will consistently meet specifications. Inter- and intra-batch variability should meet the limits as established in the PPQ protocol

c. In addition, it is expected that other attributes such as yield or expected timeframes for processing should be reviewed as indicators that the process is in a state of control

Highly variable inter or intra batch testing results, or results barely meeting specifications, may indicate an inadequately controlled process. This may mean the manufacturing process is not adequately understood and requires additional development work.

Acceptance criteria should consider the expectation that drugs be formulated to provide 100% of label claim as outlined in *Good manufacturing practices for drug products (GUI-0001)*. Additional requirements on limits of variability can be found in Sections C.01.061 and C.01.062 of the Food and Drug Regulations.

### 6.2.7 Final report

Summarize PPQ study results in a final report. The report should include (at a minimum) the following:

- references to development studies, equipment qualification reports, analytical method validation reports, and any other associated validation readiness information not included in the protocol
- reference to master production documents
- raw materials lots and testing results, where relevant (e.g. API/critical excipients)
- equipment and operating parameters, in comparison with approved parameters
- intermediate step and in-process testing results
- finished product testing results
- a discussion of inter and intra batch variability through a review of the statistical treatment of the data
- deviations, out of specification/out of trend (OOS/OOT) results and the results of the investigations. Deviations and OOS should be handled through the quality system but summarized in the report.

Your report should also include a conclusion that clearly states that the manufacturing process is considered to be one of the following:

- Qualified – The qualification study was successful. The report may recommend improvements or additional monitoring of the post-qualification batches based on the additional learning from the qualification study.
- Not qualified – The qualification study was not successful. In such cases, you must determine the cause(s) of the failure and implement appropriate remediation actions before re-executing the process qualification study. Reworking of failed qualification batches to justify their release is generally not acceptable.

It is also generally not acceptable to change protocol acceptance criteria in order to justify the successful completion of a qualification study, unless it can be shown that the change does not impact patient safety or product quality. In these cases, it would be important to discuss why the original criteria were set as they were.

### 6.2.8 Continuous process verification

The traditional approach to process validation and pharmaceutical manufacturing involves collection of samples from defined locations during batch production, which are then tested in the laboratory. This approach comes with challenges to ensure the sample is representative (see section 6.2.5Sampling and testing plan requirements) and that results are generated in a timely manner.

An option you may use when planning for process performance qualification is continuous process verification, as introduced in ICH Q8(R2): Pharmaceutical Development. It is a science and risk based approach to ensuring a manufacturing process operates within the required parameters and consistently produces material meeting specifications. Continuous process verification can make it easier to evaluate the manufacturing process, by providing more information about process variability and control.

**Continuous process verification** is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated *ICH Q8(R2): Pharmaceutical Development*.

**Note:** This term is different from the term **continued process verification** used by the US FDA *Process Validation: General Principles and Practices* to describe the ongoing monitoring phase following formal process performance qualification. The term used by the US FDA corresponds with Phase 3 in this document – Ongoing process verification.

To successfully implement a continuous process verification, you need:

- information to indicate that the manufacturing process is capable of consistently producing product meeting the QTPP
- extensive process understanding: continuous process verification is appropriate when an enhanced development approach (e.g. quality by design) has been followed, or when commercial manufacture has led to extensive process knowledge
- suitable control strategies: these can include on-line, at-line or in-line monitoring whether or not there is forward or backward feedback. Tools such as Process Analytical Technology and multivariate statistical process control are important to consider in the implementation of continuous process verification

Ensure the rationale to use continuous process verification is clearly stated and justified within development reports, submission documents and qualification/monitoring protocols.

You should determine and justify the number of batches to be assessed using continuous process verification using risk based principles. Clearly define the point at which a product will be considered to be qualified and the basis on which that decision will be made before release of batches.

A monitoring program should be implemented to monitor quality and to detect trends. A risk assessment should be performed to determine which parameters to monitor and trend. It may be necessary to implement additional controls for a period of time, when less is known about the process or when an adverse trend is suspected. A risk based approach should be used to adjust the level of effort put into the monitoring. The level of effort should reflect the level of variability and the risk of harm to the patient caused by that variability.

You can conduct continuous process verification following a holistic approach (entire manufacturing process) or hybrid approach (where it is applied to a portion of a manufacturing process, together with a traditional validation approach). It can also be introduced at any time during the lifecycle of a product.

## 6.3 Phase 3 – Ongoing process verification

Although it is expected that companies have attained a solid understanding of the manufacturing process by the time a PPQ study is initiated, it is acknowledged that product and manufacturing process knowledge will increase throughout the product's lifecycle. Continuous optimization and improvement programs based on this increased knowledge are therefore a critical part of any validation program.

Many legacy products will not have been developed and qualified in the manner outlined in this guidance. Applying the principles of Phase 3 to these products will facilitate both ensuring the process is in an adequate state of control and that process understanding increases as additional batches are manufactured.

1. A post-qualification monitoring program should be established to monitor quality and enable detection of potential trends. Post-qualification stage batch monitoring, sampling and testing requirements should be justified, representative of the entire process and statistically based (where appropriate).

2. Depending on the risk to the patient, level of variability in CQAs and confidence in the process, it may be desirable to monitor post qualification batches at an enhanced level. Testing requirements may then be re-evaluated once sufficient data has been obtained to determine estimates of process variability. Such information should be used in the determination of on-going batch monitoring, sampling and testing requirements.

3. A regular review of inter batch testing results and manufacturing parameters is instrumental in demonstrating the manufacturing process remains within a state of control. Statistical tools should be used, where appropriate, to assist in the analysis of testing results.

4. The extent and frequency of review is relative to the established level of process knowledge and confidence (i.e. newer products may require a more frequent review).

The annual product quality review (APQR) process could be sufficient for products with considerable history that have been demonstrated to be performing within a state of control.

5. The ongoing verification should be conducted in accordance with a preapproved procedure and/or protocol. Results should be summarized.

6. Where any periodic planned requalification is deemed necessary, the proposed frequency should be justified.

7. Changes in results and result trending should be investigated and actioned, where warranted. A shift in results may be indicative of a source of variability that was not previously identified, an unintended change to the process, or a need to revise control strategies.

8. The impact of a batch failure on the validation status of a product/manufacturing process should be assessed and clearly documented.

# 7. Change review

A change control system is a key GMP requirement. Use this system to evaluate changes that can potentially impact the validation status of a process/product (e.g. changes to process components, equipment, manufacturing parameters and test methods). From a validation perspective, implementing such changes could result in requirements to update product risk assessments/control strategies and/or requalify the manufacturing process.

Note: A series of minor changes over time may represent a major change requiring additional qualification.

# 8. Guidance for validation or qualification of supporting activities

This section offers specific guidance on validation and qualification activities required by GMP. The application of these sections will vary with the activity being conducted. For example, wholesalers may be concerned with fewer validation related activities such as qualification of facilities, storage and transportation equipment and systems used. It is expected that all validation and qualification work be conducted in accordance with the principles outlined in this document, i.e. that work be done according to a protocol which is developed, executed and approved by appropriate personnel with the necessary expertise, that QRM principles be taken

into account, and that all future use be considered in accordance with a change control system and lifecycle approach.

## 8.1 Facility, equipment and utility qualification

1. Ensure all equipment, facilities and utilities are appropriately qualified before use in the production of qualification/validation studies and/or commercial batches. Qualification activities should consider all stages in the lifecycle approach from initial development of the user requirement specifications through to the end of use of the equipment, facility, utility or system.

2. Qualification of facilities, utilities and equipment generally includes the following:

    a. Verifying that the proposed design of facilities, systems and equipment is suitable for the intended purpose.

    b. Verifying proper manufacture and installation in accordance with approved drawings and specifications.

    c. Ensuring that clear information is available to install, operate and maintain the facility/utility/equipment. Examples of this include manuals, drawings and standard operating procedures.

    d. Ensuring that requirements are met for proper ongoing operation of the unit/facility (e.g. calibration, preventative maintenance and training).

    e. Ensuring operation in accordance with the manner in which the system was designed including process and procedural requirements. The qualification effort should clearly demonstrate that the equipment/systems are operating in a manner that meets requirements as outlined in the user and functional requirement specifications. Operating ranges and/or worst case conditions should be challenged.

    f. Testing should also be conducted to demonstrate that equipment performs as required under actual production conditions (e.g. using production materials).

There are multiple approaches to performing qualification tasks. Each company may consider which approach works best for their operations and either approach would be deemed acceptable.

*PIC/S Annex 15: Qualification and Validation* describes distinct qualification steps, that may be conducted separately or combined as follows;

1. Design Qualification
2. Installation Qualification
3. Operational Qualification
4. Performance Qualification

The *US FDA Guidance Document - Process Validation: General Principles and Practices* and *ASTM E2500 - 13 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment* propose an approach that emphasizes careful selection, followed by verification that equipment and systems perform as intended.

3. Qualification studies should demonstrate that the systems are suitable for intended use. Manufacturer supplied qualification documents may not fully meet these requirements as the company using the equipment will be more knowledgeable of the intended use of the system.

4. Tests conducted during prequalification testing (e.g. factory acceptance testing (FAT)) may not need to be repeated during the qualification study execution if justified.

5. With respect to facility/utility qualification/validation:

    a) studies are generally required for direct contact systems (e.g. heating/ventilation/air conditioning (HVAC) or water systems) or high-risk non-contact systems

    b) ensure that the studies account for potential impact of seasonal variation

6. Conduct qualification studies according to a pre-approved protocol.

7. Maintenance events and equipment changes should be reviewed to ensure they don't impact equipment functionality or product quality.

## 8.2 Analytical Method Validation

1. Refer to *ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology* and *VICH - Analytical validation* for additional information with respect to how to conduct analytical method validation studies. Methods used to conduct release testing on commercial products must be validated.

2. Conduct analytical method validation studies according to a pre-approved protocol and summarize results in a final report. Ensure the report includes a clear conclusion.

3. Special concerns with respect to microbial testing include requirements to confirm:
    - the product formulation does not impact the recovery of microorganisms
    - residual sanitizing agents do not impact the recovery of microorganisms (environmental monitoring surface samples)

    In both cases, neutralizing agents may be required to conduct effective microbiology testing.

## 8.3 Computer System Validation

1. Computer systems should be validated to ensure that the systems operate as expected and that appropriate controls have been established for their use. For more information, please see Health Canada's adopted *PIC/S Annex 11 – Computerised Systems.*

2. In general, computer system validation should be conducted following a lifecycle method in which:
    - systems are developed in a controlled manner (e.g. user requirement specifications, functional requirement specification, design specifications)
    - qualification testing is conducted in accordance with a preapproved protocol and summarized in a final report. Factory acceptance testing and site acceptance testing may be considered in the approach to qualification.

3. The ongoing operation and configuration of the system should be monitored and reviewed at a defined frequency according to a procedure e.g. reviewing significant events/alarm logs, or user access. Use QRM principles to determine the extent and nature of effort to be required at each stage. Risk for a computerized system comes from two predominant aspects.
    - The intended use of the system.

- The nature of the system. It should be noted that custom built systems are considered to be more inherently risky than widely used commercially available systems.

4. Qualification stage testing should demonstrate that systems are appropriate for their intended use. This requires verification that the system has been installed, set-up and operates in accordance with pre-defined requirements. Ensure that system configuration and parameters are clearly documented.

5. Ensure that data control requirements are included in the computer system validation studies. The necessary system and procedural controls must be established to ensure data is maintained and protected from inappropriate modification or deletion.

## 8.4 Packaging Validation

1. Packaging qualification studies should demonstrate that the packaging process performs as intended, and ensures quality of product through shelf life.

2. In some cases, packaging operations are essential in ensuring that a product is uniform (e.g. liquid, powder and semi-solid products). Process performance qualification studies should fully assess packaging functions for such products.

3. Packaging validation needs also to confirm container integrity, and that essential labelling information such as imprinting of lot and expiry date, correct fill volume or count, leaflet insertion etc. are able to be performed correctly.

4. Sampling plans for package integrity and other critical packaging attributes should be justified based on known sources of variation in the process.

5. Primary packaging qualification should be carried out at minimum and maximum operating ranges to demonstrate their effectiveness (e.g. parameters such as temperature, machine speed and sealing pressure could be assessed for blister machines with the impact of altering each setting being adjusted). Studies should take into consideration worst case conditions of the combination of multiple operating conditions and ranges such as highest speed/lowest temperature and lowest speed/high temperature.

6. It is common in packaging processes to subject packaged product to previous steps in the process such as returning packages to the line, or repeating shrink wrapping. The impact of repeating these packaging process steps on product quality should be

assessed, for example to determine if the additional heat exposure has any effect on product quality.

## 8.5 Cleaning Validation

Information on cleaning validation requirements can be found in the *Cleaning validation guide* (GUI-0028).

# Appendices

## Appendix A – Special concerns for solid dose products

The following assumes the final dosage form is a tablet, but it also applies to other solid dosage forms, e.g. capsules, powders. It would also apply to suspension products.

Solid dose manufacturing processes should be developed in accordance with the life-cycle approach. Proper attention should be paid to ensuring that parameters impacting the product quality are understood and appropriately controlled.

Validation efforts and process performance qualification studies should generally focus on ensuring that product is uniform and meets dissolution testing requirements. This is in addition to other specific critical quality attributes that may be of concern for the product in question.

### Uniformity

Ensuring that a manufacturing process produces a uniform blend is a key consideration for a process validation study. Non-uniform blends can be caused by inadequate mixing and/or component segregation.

Proper process design is a critical attribute in ensuring uniformity.

1. The powder-blend characteristics that can affect uniformity should be understood and controlled. Examples of potential control strategies for ensuring robust powder blend characteristics include:

    - implementing controls to ensure raw material physical properties consistently meet requirements. This could involve a vendor selection program and suitable material specifications that may include non-compendial requirements (e.g. particle size profile).

    - optimizing a granulation process to account for raw material variability

2. Material segregation issues can be caused by inadequate powder-blend physical characteristics, flow problems (e.g. mass flow and arching) and excessive handling. Examples of potential control strategies to account for potential material segregation issues include:

    - improving the physical characteristics of the blend
    - reformulation to improve flow characteristics
    - re-engineering systems to improve material flow (e.g. different angles, openings and materials) and to minimize the amount of material handling and movement (e.g. use of one bin to prevent material transfer and/or minimizing distance between the bin and press)

The assessment of blend uniformity normally includes two steps: a blend uniformity assessment and a content uniformity assessment. Sampling from bins may also be required after the discharge step has been completed.

1. Blend uniformity assessment: Obtain samples from the blender at the completion of the mixing process. Evaluate results to ensure the blend is well mixed and that no significant difference exists between locations in the blender that could adversely affect product quality. Criteria to be evaluated include:
    a. Blend uniformity sample size: Blend uniformity samples should be 1 to 3 times the minimum dosage size being evaluated. You may use larger samples with justification.
    b. Sampling locations: Sampling locations should enable full assessment of the blender and include potential problem areas (e.g. dead spots). Use statistical tools to determine the number of replicates to be obtained and the number of sampling locations within the blender
    c. Sampling method: Sample thieves remain widely used and can—in many cases—present acceptable results. However, they do have drawbacks because they cause bed disturbance so sampling errors are possible. Evaluate the reliability of sampling as part of the analytical method development.
    d. Testing requirements: Determine the number of replicate samples to be analyzed from each location. Testing more than one replicate sample has the benefit of helping to determine whether you have location to location variation or within location variation. Regardless of how many samples are taken, each sample should be tested separately. Combining doses as a composite for a single analytical determination is not appropriate.
    e. Acceptance criteria: Pre-establish acceptance criteria and base it on a statistical analysis.

Health Canada recommends that you consider innovative approaches to assessing the adequacy of mixing of powder blends. Some methods of doing this include:

- process analytical technology (PAT)
- the use of statistical process controls

If you decide to implement PAT or other process-monitoring and control techniques for a powder blend homogeneity assessment, your decision should be supported with appropriate data and rationale, using both a science and risk-based approach.

2. Content uniformity assessment: Content uniformity involves obtaining samples from the tablet press (or dosing machine). The process performance qualification protocol should define:
    - sampling times, ensuring that worst case locations such as first and last accepted tablets are included
    - number of tablets or capsules to be sampled at each location
    - acceptance criteria

    It is expected that no significant differences would exist between in-process locations that could affect finished product quality. Between- and within-location variability is a critical component of the finished product quality, so should be evaluated. All such evaluations should be statistically based and scientifically justified. Examples of acceptable statistical methods are outlined in *ASTM E2709* and *ASTM E2810*.

Investigate out-of-specification uniformity testing results according to your firm's deviation investigation procedure. Discuss such a failure in the final report, with a summary of actions taken to address the situation and the overall impact of the failure on the qualification study.

## Dissolution

It is important to understand the factors that will control the overall dissolution rate before beginning the process performance qualification study. For example:

1. Formulation variables - Ensure formulation components used to control dissolution rates are understood and well controlled, such as:
    a. impact of levels of excipients such as disintegrant, binder, lubricant etc.

b. impact of control releasing polymers or functional film coatings. Additional controls of functional tablet coating processes may be required in comparison to a normal film-coated (non-functional) coating.

2. Manufacturing process variables such as:

   a. lubrication mix time can impact dissolution rates, for example for immediate release tablets
   b. tablet hardness can impact the tablet dissolution rate. Conduct hardness studies (where tablet hardness and dissolution rates are compared/correlated) as part of the development process. Establish hardness specification and guideline tablet press settings (e.g. feeder type/speed, compression speed, pre-compression force and main compression force) before starting the process qualification effort.

The impact of any formulation and manufacturing parameter variability on dissolution rates should be understood during Phase 1 and appropriate controls should be established.

You may be required to demonstrate that the dissolution profile of commercial lots is similar to that of the bio lot or submission profile. Any approach used to demonstrate similarity should be statistically justified. One such example is the use of a similarity factor (f2), in which an f2 value of between 50 and 100 is considered to be indicative of a similar dissolution profile.

It is important to note that dissolution profile testing should be conducted on samples obtained from across the batch.

For more information on conducting similarity calculations, see Health Canada's *Post-Notice of Compliance (NOC) Changes: Quality Document, "Appendix 5 – Recommendations for conducting and assessing comparative dissolution profiles"*.

# Appendix B – Glossary

## Acronyms

| | |
|---|---|
| API: | Active pharmaceutical ingredient |
| APQR: | Annual Product Quality Review |
| CPP: | Critical process parameters |
| CQA: | Critical quality attributes |
| EMA: | European Medicines Agency |
| FAT: | Factory acceptance testing |
| GMP: | Good manufacturing practices |
| HVAC: | Heating/ventilation/air conditioning |
| ICH: | International Council for Harmonisation |
| OOS: | Out of specification |
| OOT: | Out of trend |
| PAT: | Process analytical technology |
| PIC/S | Pharmaceutical Inspection Co-operation Scheme |
| PPQ: | Process Performance Qualification |
| QRM: | Quality Risk Management |
| QTPP: | Quality target product profile |
| US FDA: | United States Food and Drug Administration |
| WHO: | World Health Organization |

# Terms

These definitions explain how terms are used in this document (unless otherwise specified). Definitions cited directly from other documents are noted in brackets at the end of the definition.

If there is a conflict with a definition in the *Food and Drugs Act* or Food and Drug Regulations, the definition in the Act/Regulations prevails.

**Change control –** 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 a quality or support system. (GUI-0001)

**Concurrent Validation -** Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches. (PIC/S Annex 15 – PE 009-14 (Annexes))

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

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

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

**Design Qualification –** The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose. (PIC/S Annex 15 – PE 009-14 (Annexes))

**Drug** – Includes any substance or mixture of substances manufactured, sold or represented for use in:

*(a)* the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
*(b)* restoring, correcting or modifying organic functions in human beings or animals, or
*(c)* disinfection in premises in which food is manufactured, prepared or kept;

(Section 2 of the *Food and Drugs Act*)

From Division 1 A of the Food and Drug Regulations (C.01A.001);
(2) In this Division and in Division 2, drug does not include any of the following:
(a) a dilute drug premix;
(b) a medicated feed as defined in subsection 2(1) of the Feeds Regulations, 1983;
(c) an active ingredient that is for veterinary use and that is not an active pharmaceutical ingredient;
(d) an active pharmaceutical ingredient for veterinary use that is not required to be sold pursuant to a prescription and that is also a natural health product as defined in subsection 1(1) of the Natural Health Products Regulations;
(e) a drug that is used only for the purposes of an experimental study in accordance with a certificate issued under section C.08.015.

Installation Qualification – The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations. (PIC/S Annex 15 – PE 009-14 (Annexes))

Lifecycle – All phases in the life of a product from the initial development through marketing until the product's discontinuation. (ICH Q8)

Operational Qualification – The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges. (PIC/S Annex 15 – PE 009-14 (Annexes))

Performance Qualification – The documented verification that systems and equipment can perform effectively and reproducibly based on the approved process method and product specification. (PIC/S Annex 15 – PE 009-14 (Annexes))

Process analytical technology (PAT) – A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. (ICH Q8)

Process qualification – Confirming that the manufacturing process as designed is capable of reproducible commercial manufacturing. (*Process Validation: General Principles and Practices | US FDA*)

**Process validation –** The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products (*Process Validation: General Principles and Practices | US FDA*)

**Prospective Validation –** Validation carried out before routine production of products intended for sale. (PIC/S Annex 15 – PE 009-14 (Annexes))

**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)

**Risk –** The combination of the probability of occurrence of harm and the severity of that harm. (ICH Q9)

**Risk assessment –** A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of the hazards and the analysis and evaluation of the risks associated with exposure to those hazards. (ICH Q9)

**Risk management –** The systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk. (ICH Q9)

**State of control –** A condition in which the set of controls consistently provides assurance of acceptable process performance and product quality. (ICH Q10

**Trend –** A statistical term referring to the direction or rate of change of a variable(s). (ICH Q9)

**Unit operation –** A single step or stage within a manufacturing process.

**User requirements specifications –** The set of owner, user, and engineering requirements necessary and sufficient to create a feasible design meeting the intended purpose of the system. (PIC/S Annex 15 – PE 009-14 (Annexes))

**Validation –** A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria. (ICH Q7)

**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.

# Appendix C – References

## Laws and regulations

*Food and Drugs Act*
laws-lois.justice.gc.ca/eng/acts/f-27/

Food and Drug Regulations
laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html

## Health Canada guidance

*Annex 7 to the Good manufacturing practices guide for drug products – Selected non-prescription drugs (GUI-0066)*
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/annex-7-good-manufacturing-practices-guide-drug-products-selected-non-prescription-drugs-0066.html

*Cleaning validation guide (GUI-0028)*
www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/cleaning-validation-guidelines-guide-0028.html

*Good manufacturing practices guide for drugs (GUI-0001)*
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/good-manufacturing-practices-guidelines-2009-edition-version-2-0001.html

*Guidance Document: Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)*
www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-document-quality-chemistry-manufacturing-guidance-new-drug-submissions-ndss-abbreviated-new-drug-submissions.html

*Guidance Document: Addendum - Quality (Chemistry and Manufacturing) Guidance: Questions and Answers*
www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-document-addendum-quality-chemistry-manufacturing-guidance-questions-answers.html

Guidance Document *Post-Notice of Compliance (NOC) Changes: Quality Document*
https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/quality-document.html

*Process Validation: Gaseous Sterilization for Pharmaceuticals (GUI-0007)*
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/gaseous-sterilization-pharmaceuticals.html

*Process Validation: Irradiation Sterilization for Pharmaceuticals (GUI-0009)*
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/irradiation-sterilization-pharmaceuticals.html

*Process Validation: Moist Heat Sterilization for Pharmaceuticals (GUI-0010)*

https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/moist-heat-sterilization-pharmaceuticals.html

## US FDA guidance

*FDA Guidance for Industry - Process Validation, General Principles and Practices*
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/process-validation-general-principles-and-practices

*FDA Guidance for Industry: SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (November 1995)*
www.fda.gov/regulatory-information/search-fda-guidance-documents/supac-ir-immediate-release-solid-oral-dosage-forms-scale-and-post-approval-changes-chemistry

*FDA Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (October 1997)*
www.fda.gov/regulatory-information/search-fda-guidance-documents/supac-mr-modified-release-solid-oral-dosage-forms-scale-and-postapproval-changes-chemistry

## ICH guidance

*ICH Q2: Validation of Analytical Procedures: Text and Methodology*
www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/validation-analytical-procedures-text-methodology.html

*ICH Q5C: Quality of Biotechnological Products: Stability Testing of biotechnological Biological Products*
www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/quality-biotechnological-products-stability-testing-biotechnological-biological-products-topic.html

*ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*
https://ich.org/page/quality-guidelines

*ICH Q8 (R2): Pharmaceutical Development*
www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/pharmaceutical-development-topic.html

*ICH Q9: Quality Risk Management*
www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/adoption-international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use.html

*ICH Q10: Pharmaceutical Quality System*
www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/adoption-international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-guidance-pharmaceutical-quality-system.html

*ICH Q11: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)*
www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/development-manufacture-drug-substances-chemical-entities-biotechnological-biological-entities-topic.html

## European Medicines Agency guidance

*EMA Guideline on process validation for finished products-information and data to be provided in regulatory submissions*
https://www.ema.europa.eu/en/process-validation-finished-products-information-data-be-provided-regulatory-submissions

## Other guidance

*ASTM E2500 - 13 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment*
www.astm.org/Standards/E2500.htm

*ASTM International: ASTM E2709 Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure*
www.astm.org/Standards/E2709.htm

*ASTM International: ASTM E2810: Standard Practice for Demonstrating Capability to Comply with the Test for Uniformity of Dosage Units*
www.astm.org/Standards/E2810.htm

*Glossary and Tables for Statistical Quality Control,* Fourth Edition, American Society for Quality Control, Statistics Division, ASQ Quality Press, 2004.

*Parenteral Drug Association Technical Report 60 Process Validation: A Lifecycle Approach (2013)*
www.pda.org/publications/pda-publications/pda-technical-reports

*Pharmaceutical Inspection Cooperation Scheme Annex 11: Computerized Systems*
https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/annex-11-computerized-systems.html

*Pharmaceutical Inspection Cooperation Scheme Annex 15: Qualification and Validation (PE 009-14)*
www.picscheme.org/en/publications

*VICH GL2: Validation of Analytical Procedures - Methodology*
www.vichsec.org/en/guidelines/pharmaceuticals/pharma-quality/analytical-validation

*WHO General Guidance on Hold Time Studies*
https://apps.who.int/iris/handle/10665/176954