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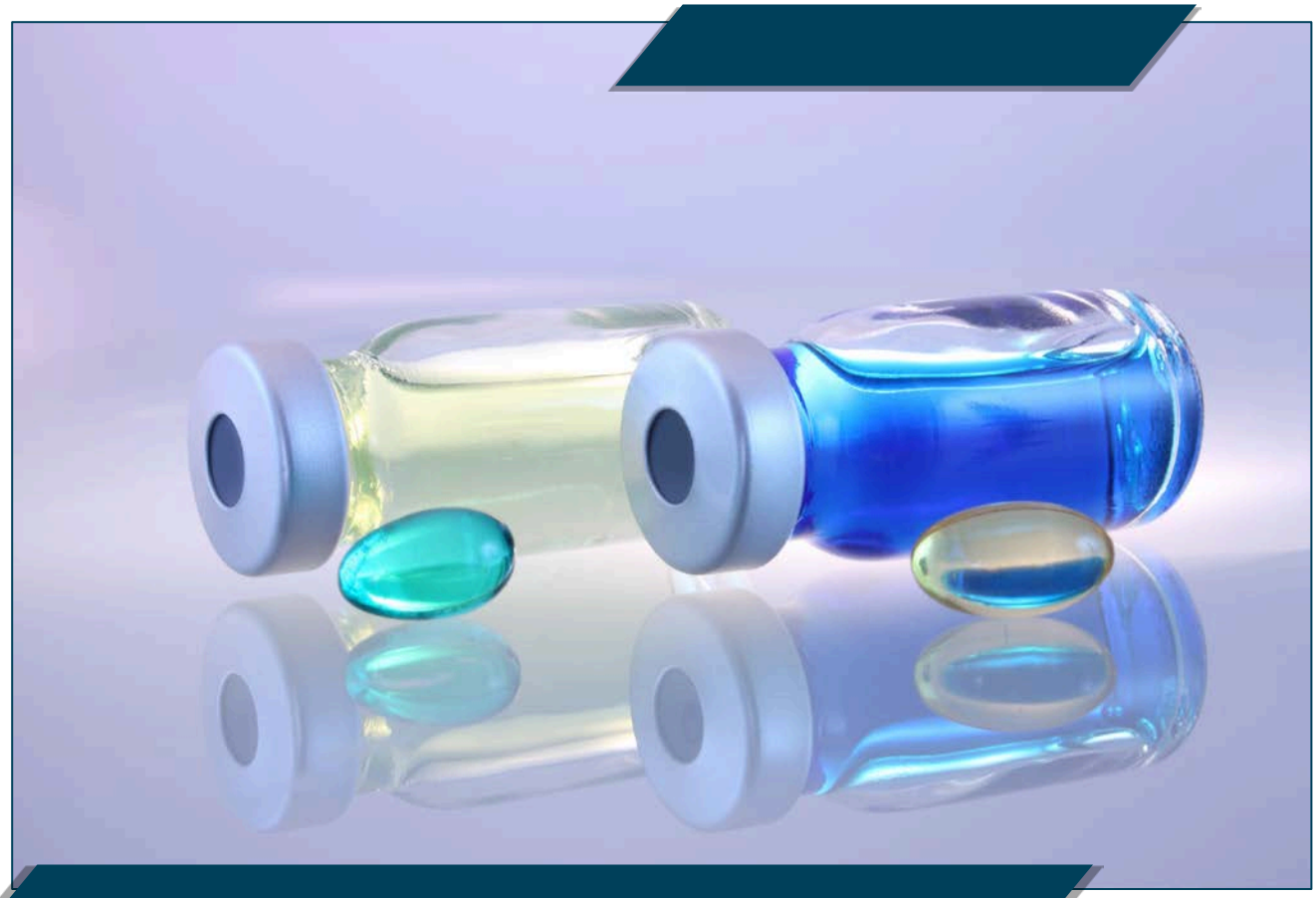
Cleaning validation guide



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Cleaning validation guide (GUI-0028)

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Ce document est aussi disponible en français.

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1. Purpose

This document is for anyone involved in pharmaceutical, biological and radiopharmaceutical manufacturing and regulations in Canada, including:

- regulated industry
- inspectors and evaluators

It provides guidance on cleaning validation. It will help you understand and comply with Part C, Division 2 of the Food and Drug Regulations, (the Regulations).

This guide is also intended to establish inspection consistency and uniformity with respect to equipment cleaning procedures. Principles incorporated in international guidance have been taken into account when preparing this document.

The recommendations in this guide are not requirements under all circumstances. Inspectors, evaluators and industry may consider other approaches if documented with proper scientific justification.

2. Scope

This guide addresses special considerations and issues when validating cleaning procedures for equipment used to fabricate and package:

- active pharmaceutical ingredients (APIs)
- pharmaceuticals
- radiopharmaceuticals
- biological drugs

It covers validation of equipment cleaning for:

- the removal of contaminants associated with products used in the previous production run, residues of cleaning agents, and processing agents
- the control of potential microbial contaminants

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 Health Canada conducts an inspection, inspectors will use this document as a guide in assessing the site's compliance with GMP requirements with respect to equipment cleaning.

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 taken.

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.

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.

Guidance

4. Principles

Cleaning validation is performed to ensure that the cleaning process will consistently reduce the possibility of cross contamination in a drug manufacturing process. It provides documented evidence that an approved cleaning process will reproducibly remove the previous products or cleaning agents used in the equipment to below scientifically set maximum allowable carry-over levels (MACO).

All product-contact equipment cleaning processes must be validated. Consideration (based on risk) should also be given to non-contact parts from which product may migrate.

Implement remediation actions if a cleaning process is not capable of consistently producing adequate results. Examples of remediation actions include improved cleaning procedures and equipment/facility dedication. Continued cleaning failures and/or testing until clean (i.e. continually cleaning and testing until acceptable results are achieved) are not acceptable.

It is also important to ensure equipment and facility design, cleaning, storage and use are appropriately controlled to prevent microbial contamination of products.

5. Applying quality risk management (QRM) to control cross-contamination risks

1. Cleaning and cross contamination risks should be assessed via a documented QRM process. The QRM process should evaluate such risks based on scientific knowledge and assessment. All actions taken should be at a level proportional to the identified risks.

The following describes the technical and organizational measures that should be implemented in response to the QRM process. Please refer to the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to good Manufacturing Practice for Medicinal Products Part I, Chapter 5.

2. The outcome of the QRM process should be the basis for determining the extent of the technical and organizational measures required to control risks for cross-contamination. These could include technical measures and organizational measures.

   a. Technical Measures include:

   i. Dedicated manufacturing facility (premises and equipment).
   ii. Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas.
   iii. Design of manufacturing process, premises and equipment to minimize opportunities for cross-contamination during processing, maintenance and cleaning.
   iv. Use of "closed systems" for processing and material/product transfer between equipment.
   v. Use of physical barrier systems, including isolators, as containment measures.
   vi. Controlled removal of dust close to source of the contaminant e.g. through localized extraction.
   vii. Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools.
   viii. Use of single use disposable technologies.
   ix. Use of equipment designed for ease of cleaning.
   x. Appropriate use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area.
   xi. Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air.
   xii. Use of automatic clean in place systems of validated effectiveness.
   xiii. For common general wash areas, separation of equipment washing, drying and storage areas.

   b. Organizational measures include:

i. Dedicating the whole manufacturing facility or a self-contained production area on a campaign basis (dedicated by separation in time) followed by an effective, validated cleaning process.
ii. Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed.
iii. Cleaning verification after each product campaign should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach for products deemed to present higher risk.
iv. Depending on the contamination risk, verification of cleaning of non-product contact surfaces and monitoring of air within the manufacturing areas and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer.
v. Specific measures for waste handling, contaminated rinsing water and soiled gowning.
vi. Recording of spills, accidental events or deviations from procedures.
vii. Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk.
viii. Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas.
ix. Use of common general wash areas on a campaign basis.
x. Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.

3. Measures to prevent cross-contamination and their effectiveness should be reviewed periodically according to set procedures.

6. Cleaning validation master plan

1. You should maintain a Cleaning Validation Master Plan (or equivalent document) to outline the general cleaning validation policies at your site.

2. Product and equipment may be grouped in accordance with QRM principles:

    a. You may choose to conduct cleaning validation studies on all products at the facility or on worst case products only (i.e. product family approach). Stipulate (and justify if required) which approach is being used in the Cleaning Validation Master Plan Document the following if a worst case approach is being used:

        - The methodology/scientific rationale used in determining the worst case products.

- The actual worst case products. Include a listing of all products in relation to the identified worst case products.

Examples of factors that can be included in the assessment of worst case products include:

- Difficulty in cleaning
- Solubility of residues in cleaning agents and water
- Physical characteristics of the product, active pharmaceutical ingredient and excipients
- Potency and toxicity of the API
- Past experience (e.g. during development and with similar products)

There may be multiple worst case products.

You may choose to conduct cleaning validation studies for all equipment or by representative equipment trains only. A representative approach is suitable if equipment is similar in terms of size, design, function and clean-ability. Document the following if an equipment grouping approach is being used:

- The approach/scientific rationale by which equipment were grouped together.
- A listing of all equipment in each group. Identify the equipment in each group that is considered to be worst case (with justification).

3. All cleaning processes must be equivalent if cleaning validation studies are to be conducted following a worst case product and/or equipment grouping approach.

7. Cleaning validation lifecycle approach

Validation, in a lifecycle approach, involves the collection and evaluation of data throughout the product's lifecycle. Learnings from each stage are critical in ensuring appropriate controls are established. For cleaning validation, the lifecycle approach normally involves the following steps:

- Step 1 - Cleaning process design and development: Develop effective cleaning procedures in a controlled and documented manner prior to implementation in the manufacturing plant.
- Step 2 – Cleaning Process qualification: Evaluate cleaning processes to ensure they are effective and reproducible. Cleaning process studies involve conducting cleaning verification assessments a predetermined number of times under specified conditions.
- Step 3 – On-going monitoring: Ensure cleaning procedures remain effective and controlled via an ongoing monitoring program.

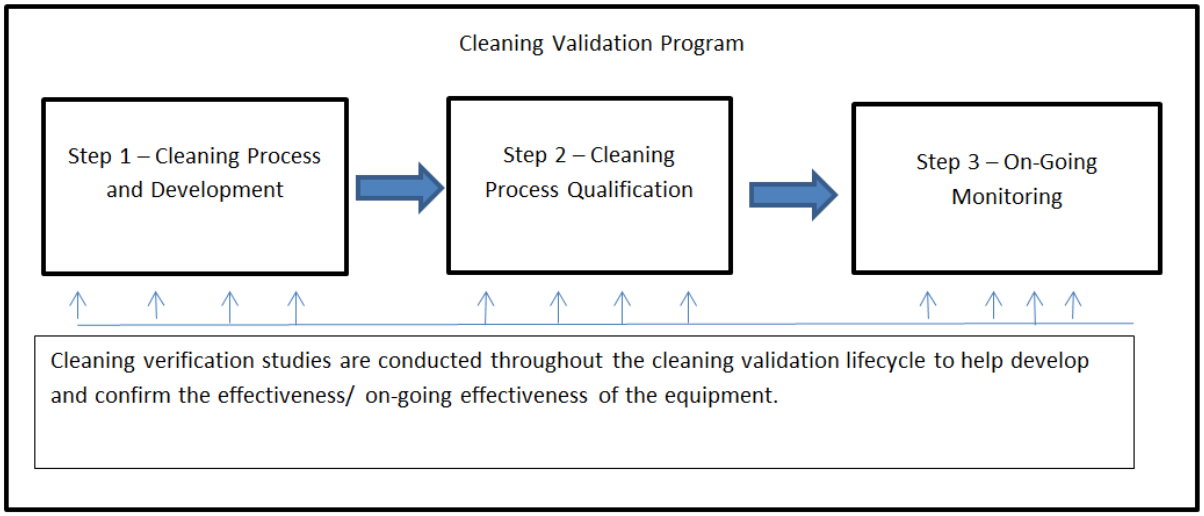
It is important to differentiate between three important terms with respect to where they fit into the overall cleaning lifecycle approach.

Cleaning verification refers to the gathering of evidence through chemical analysis after each batch/campaign to show that the residues of the previous product or cleaning agents have been reduced below pre-defined acceptable criteria such as scientifically set MACO.

Cleaning verification refers to the actual assessment of equipment cleanliness and is used throughout the cleaning lifecycle approach. Cleaning verification is used to verify that individual equipment has been appropriately cleaned and release the equipment to be used in the manufacture of subsequent products and batches.

Cleaning process qualification refers to a defined step within the cleaning validation lifecycle. It will normally be comprised of multiple cleaning verification assessments for all equipment involved in the cleaning validation study. Refer to Section 5.2 for additional information.

Cleaning validation refers to the overall validation program, from the development stage all the way through the ongoing monitoring stage. The cleaning validation program is comprised of the result of appropriately controlled cleaning procedures and having appropriate data to demonstrate their effectiveness.



7.1 Step one – Cleaning process design and development

- Cleaning procedures are developed in a controlled manner to ensure cleaning processes are effective and reproducible.
- It is important that an understanding of potential issues that could impact cleaning processes and overall consistency be considered when developing new cleaning processes. Items for consideration include potential degradant formation and variability in raw materials.
- Ensure appropriate effort and resources are applied when designing and developing new cleaning processes. This could include laboratory trials, cleaning trials and the evaluation of cleaning effectiveness after the manufacture of development/pre-commercialization batches. Document learnings during the cleaning development process to ensure knowledge transfer.

7.1.1 Introducing new products to a facility

Assess the clean-ability and potential risks associated with new products being introduced into your facility. Consider the following:

- The suitability of the product for your facility and whether dedicated facilities/equipment or other additional controls are required.

- If the product is a worst case product (this is especially critical if a worst case cleaning validation approach is being followed).

- If existing cleaning processes are adequate or if a new process is required.

Verification studies will normally be used to demonstrate equipment has been adequately cleaned in situations in which non-commercial products (e.g. development, technology transfer and clinical trial batches) are produced using commercial equipment. The verification studies can be used to release equipment for the manufacture of subsequent products and provide valuable data in the development of cleaning processes.

Ensure that cleanings are conducted in accordance with an appropriately detailed cleaning Standard Operating Procedure.

Ensure that cleaning verification studies are conducted in accordance with a protocol (or equivalent document) and results should be summarized in an appropriate manner.

Ensure the evaluation for equipment release at this stage is, at a minimum, equivalent to the cleaning evaluation during the qualification stage.

7.1.2 Control of cleaning processes

The outcome of the design and cleaning development process should be a defined cleaning process that is both reproducible and effective. Factors that can influence cleaning effectiveness should be identified and controlled.

Ensure manual cleaning procedures are consistently performed by:

a. Having adequately detailed instructions and establishing range/value of the critical process parameters:
    i. sequence of the cleaning steps
    ii. cleaning agent to be used and its concentration
    iii. cleaning agent application means (e.g. soaking or scrubbing)
    iv. contact time
    v. temperature of the cleaning solutions and rinses
    vi. rinsing techniques (soaking, flushing, times and pressures)
b. Establishing and maintaining operator training and certification programs. It is not acceptable to repeatedly blame cleaning failures on inappropriate cleaning techniques (i.e. operator error), as this indicates inadequate control.

c. Ensuring that cleaning procedures are adequately documented and that calibrated measuring devices (such as timers, temperature probe, dosing pump and flow meter), if required, are used.

d. Ensuring operator consistency is one of the biggest challenges in a manual cleaning program. The Quality Risk Management evaluation should clearly identify steps required to ensure both consistency in how the procedures are conducted and the overall outcome of the cleaning validation process.

Control automated cleaning equipment (e.g. Clean-In-Place) and processes by:

e. Having adequately detailed procedures to describe the automated cleaning and any other relevant factors (e.g. equipment preparation or disassembly).

f. Qualifying equipment used for such cleaning including verification that all product contact surface areas are being appropriately contacted by the cleaning/rinsing agents.

g. Ensuring that appropriate calibration and maintenance programs are established and maintained.

h. Defining cleaning sequences (including all temperatures, concentrations, valve openings, spray rates, pressures and volumes). It is also important to ensure that cleaning sequences (e.g. automated recipes) are appropriately protected against unapproved or uncontrolled changes.

i. Monitoring critical control points and parameters with appropriate sensors and alarms to ensure the process is highly controlled. Critical alarms should be identified and regularly challenged if required. Procedures should outline steps to be taken in response to such alarms.

j. Ensuring cleaning sequences and data — including alarms — are appropriately controlled and reviewed.

7.2 Step 2 - Cleaning process qualification

1. You may begin a cleaning process qualification study once you have a fully defined cleaning process. This can be before the start of commercial production if equipment, batch sizes, and formulation/operating parameters are not subject to change.

Cleaning process qualification studies must be available for all products (or worst case products if a product family approach is used). It is understood that it may take time to assess the requisite number of batches.

The cleaning process qualification study should be, at a minimum, started when commercial production is initiated. Equipment can be released for further manufacturing after passing cleaning verification results are obtained.

Note: If a worst case approach is being followed and the study is ongoing, you must ensure adequate data is available to support the cleaning of non-worst case products.

2. Use QRM principles to determine the extent and scope of cleaning process qualification requirements:
    a. Determine the number of cleans to be assessed using a documented risk assessment. Although a three-clean assessment has long been the industry norm, your risk assessment may result in qualification studies that require you to evaluate a different number of cleans.
    b. You may also incorporate worst case condition challenge testing (e.g. minimum detergent contact time, minimum or maximum temperatures and minimum rinse time/volume/pressure). Worst case challenge testing is of particular importance when manual cleaning systems are employed.
    c. Other challenge tests may also be required (e.g. having multiple operators across different shifts conduct the cleaning when manual cleaning processes are being used).

3. Document the cleaning process qualification requirements in a protocol. The protocol should include:
    a. responsibilities for performing and approving the qualification study
    b. description of the equipment to be used
    c. references and descriptions of the cleaning parameters to be used
    d. any worst case challenge plans to be evaluated in the study
    e. the number of cleaning cycles to be performed subsequently (i.e. individual cleans should not be missed or not incorporated in the cleaning validation study while the study is ongoing)
    f. sampling procedures, including the rationale for why a certain sampling method is used
    g. clearly defined sampling locations

h. validated analytical methods, including the limit of detection and the limit of quantitation of those methods and data on recovery studies

i. the acceptance criteria, including the rationale for setting the specific limits

4. Ensure you have data to demonstrate the following does not impact cleaning performance:

    a. The length of time between the completion of manufacturing and start of cleaning (dirty hold time).

    b. The maximum allowable number of batches manufactured prior to full cleaning (specify maximum campaign lengths in days and/or number of batches).

5. Investigate any cleaning failure as per quality system requirements.

6. Prepare a final qualification report. The conclusions of this report should state if the cleaning process has been qualified successfully.

7. Separate sections within this guide detail analytical method control, equipment sampling and acceptable carryover calculation requirements.

7.3 Step 3 - On-going monitoring

1. Conduct additional monitoring after the completion of the cleaning process qualification study to demonstrate the process remains in a state of control. Use QRM principles to determine the frequency of such monitoring.

2. Areas of special concern, in terms of on-going monitoring, include:

    a. manual cleaning processes

    b. highly potent and toxic products

    c. equipment and products with a history of failure and/or highly variable testing results during verification and qualification testing

    d. location or surface that are difficult to access or clean

    e. equipment and products which cannot be appropriately visually inspected

Refer to Section 4 for additional considerations in terms of assessing on-going monitoring requirements.

7.3.1 Change control and requalification

1. Ensure a change control system is in place to assess and document all changes that might impact the cleaning process. The review should include consideration of whether the cleaning procedure should be re-developed and/or re-qualified.

2. Changes that may potentially impact cleaning processes include:
    a. new products
    b. changes to the cleaning process
    c. changes in the formulation and/or process of products
    d. raw material changes (e.g. change in impurity profile or physical properties)
    e. new cleaning agents and/or changes in cleaning agent formulation
    f. significant equipment changes or new equipment.
    g. lot size or campaign length changes
    h. changes in analytical procedures

Note: The installation of used equipment (i.e. equipment sourced from other sites) may pose special challenges in terms of ensuring the cleanliness of such equipment is appropriately evaluated prior to use. This should be considered per QRM principles.

8. Analytical methods

1. Validate analytical methods used to measure equipment residue and contaminants (e.g. product active drug, degradants and detergent residue).

Refer to ICH Q2 for general information with respect to how to validate analytical methods.

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

3. Conduct recovery studies for all cleaning analytical and sampling methods:

Recovery studies demonstrate that the sampling (see section 7) and analytical methods can adequately measure residue that may be present on equipment surfaces. Such studies are performed by spiking material coupons with the residue under consideration at low levels representative of amounts after cleaning. Sampling the residue according to the applicable method. Testing results should then be compared with the actual quantity spiked onto the coupon.

- Ensure the sampling method used in the laboratory is equivalent to the method used in manufacturing.
- Conduct recovery studies for all applicable product contact surfaces.
- Establish recovery correlation coefficients for each product contacting surfaces and use them in the calculation of residual contaminants.
- Low or variable recovery of standards may not be acceptable as it is indicative of an inadequate sampling or extraction techniques.
- Non-specific analytical methods (e.g. Total organic carbon (TOC) and conductivity) may be used with appropriate justification. In such cases, you must establish the

correlation between testing result and the concentration of the product. You must assume that the testing result is entirely due to the target residue in such cases. Companies must still demonstrate that the sampling method will provide adequate and reproducible recovery.

Note: It is recommended that investigations into failures quantify the exact amount of the analyte under question and attempt to quantify any other sources of potential contamination.

9. Assessment of cleaning

9.1 Visual inspection

Visual inspection is a qualitative method to determine equipment cleanliness and involves the inspection of equipment for the absence of visible residue and foreign material. This is an important element of any cleaning program.

1. Conduct spiking studies to determine the concentration at which most active ingredients are visible. This is an important consideration as visual inspection alone may not be adequate if the product is not visible at concentration levels that may pose a risk to patient safety (e.g. below the calculated MACO value).

2. Investigate visual inspection failures through their applicable Quality System. Visual inspection failures should be rare when a cleaning process has been validated and may be indicative of an inadequately controlled cleaning process.

3. Conduct visual inspections after all cleans and document the results.

4. Investigate visual inspection failures per quality system requirements.

5. Conduct visual inspections before conducting any cleaning verification/qualification/on-going monitoring sampling activities.

6. Ensure visual inspection is only conducted by qualified personnel. Have a program in place to assess the effectiveness of personnel conducting the visual inspections.

7. Establish procedures detailing how visual inspections are to be conducted. Include clear instructions with respect to:
    i. disassembly instructions
    ii. use of an appropriate light source/appropriate lighting conditions
    iii. how to assess difficult areas (e.g. bottom of mixing blades)

9.2 Equipment sampling

Equipment sampling is generally conducted via direct surface sampling (swab/wipe method), rinse sampling or a combination of the two. See below for more information.

9.2.1 Direct surface sampling (swab/wipe method)

Swab sampling involves wiping an equipment surface with a specified material to recover residue from the surface. The material is then placed in a solvent to transfer the residue from the material into the solvent.

a. Conduct swab/wipe sampling on hardest to clean areas. Clearly specify hardest to clean areas in relevant protocols. Consider the following when determining hardest to clean areas:
    - accessibility
    - equipment geometry
    - potential for residue accumulation
    - material of construction

b. Specify the material to be used for swabbing and the sampling medium (solvent).

c. Ensure production equipment is sampled in the same way as during recovery studies in the laboratory. Measures to ensure consistency in swabbing include detailed procedures and training/certification of personal conducting the swabbing (both in the laboratory and in manufacturing).

9.2.2 Rinse sampling

Rinse sampling involves rinsing the relevant equipment surfaces with a specified sampling agent to remove residue. Measure the residue levels in the rinsing liquid. Rinse samples allow the sampling of a large surface area and of systems that are inaccessible or cannot be routinely disassembled.

9.2.3 Placebo sampling

1. Placebo sampling is another alternative that can be used for assessment of cleaning effectiveness. Placebo sampling involves the processing of a placebo batch after cleaning activities have been completed and then analyzing the placebo for traces of the previous product. Such evaluations are normally conducted to complement swab and/or rinsing studies.

10. MACO calculations

The allowable amount of residue allowed on equipment and/or a process train after cleaning is referred as a MACO value.

1. Ensure the rationale for choosing limits for residues is scientifically justified based on the materials involved and their allergenicity, toxicity, potency and minimum therapeutic dose.

2. Use risk management principles when determining maximum allowable carryover calculations for active ingredients and detergent levels. Such limits should be based on toxicological evaluation and documented in the form of a risk assessment.

3. Ensure the limits are practical, achievable and verifiable. If this is not possible, consider alternative means of risk reduction such as equipment dedication.

You may refer to the PIC/S Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. Companies should ensure any alternative approaches are appropriately justified.

In addition, companies should consider employing traditional measures of cleaning (1/1000th of a dose and 10 ppm) as alert limits. Cleaning procedures have traditionally been established as being able to meet such limits.

4. Calculated cleaning acceptance criteria should be establishing accounting for the cumulative impact of residue from multiple shared equipment (i.e the process train effect).
    a. recommended that residue limits be set for each individual piece of equipment.

11. Microbiological controls

1. Ensure that equipment and facility design, operation, cleaning and maintenance will appropriately control microbiological bioburden. Focus on preventative measures rather than removal of contamination once it has occurred.

2. Use QRM principles to determine:

    a. The need for including microbiological and/or endotoxin contamination evaluating as part of verification/qualification and on-going monitoring assessments.

    b. The type, nature and scope of an ongoing environmental monitoring program.

3. Areas of special concern for microbiological considerations include:

    a. Clean hold times: Establish a maximum period of time that cleaned equipment can sit after storage before use without re-cleaning or re-sanitization. Demonstrate that the maximum allowable clean hold time storage does not result in microbial proliferation.

    b. Ensure that microbiological assessments are considered (per risk management principles) when assessing maximum campaign lengths.

    c. Ensure that stagnant water is not allowed to remain in equipment after cleaning or use. Equipment should be dried before use or storage.

    d. Ensure that procedures are established for the appropriate handling of hoses. Hoses (e.g. purified water hoses) are a known area of potential microbial contamination.

4. Ensure that microbiological limits are scientifically justified.

12. General equipment cleaning considerations

Ensure all processing equipment is designed to facilitate cleaning and permit visual inspection (where possible). They should have smooth surfaces and be made of non-reactive materials. Piping of the equipment should be sloped continuously to ensure adequate drainability of the lines. Deadlegs should be avoided. For long transfer lines, consider removable sections to evaluate the efficacy of the cleaning process by visual, swab testing and/or rinse sample.

12.1 Cleaning agents:

1. When using cleaning agents, ensure that their composition is known and that you are notified of any changes in the cleaning agent.

2. Ensure that cleaning agents are easily removable.

Removal of cleaning agents is an important consideration in any cleaning validation program. Evidence should be available that cleaning procedures will effectively remove cleaning agents to below predetermined levels.

12.2 Last rinse:

1. If water is used to perform the last rinse ensure it is equivalent to the grade and standard of water being used in the product formulation. Water quality parameters (i.e. chemical, microbiological and endotoxin) should be appropriate for the given application.

2. If the cleaning procedure requires a solvent as the last rinse, the quality of the solvent should be appropriate.

Use water-for-injection as the last rinse for product-contact equipment used to manufacture sterile injectable products. You may use purified water as the last rinse for product-contact equipment used to manufacture non-sterile products or sterile products for ophthalmic use.

12.3 Dedicated equipment and facilities:

Dedicated equipment may be required for the production of some products. Examples of reasons you may decide to dedicate equipment include potent/toxic products, the potential for allergic reactions and/or sensitization and products which are extremely difficult to clean. Product dedication may also be appropriate, in some instances, for

equipment parts which are either difficult to clean, sample or visually inspect (especially for higher risk products).

Use QRM principles to determine cleaning validation requirements and MACO values. Areas of concern with dedicated equipment include:

a. microbiological considerations
b. cleaning agent removal
c. potential product degradants and process impurities
d. the effectiveness of visual inspection

Self-contained facilities are required when a product presents a risk:

- that cannot be properly controlled by operational and/or technical measures
- where scientific data does not support a safe threshold value for toxicity
- where threshold values derived from the toxicological evaluation are below the levels of detection
- for certain classes of highly sensitizing drugs (such as penicillins and cephalosporins)

13. Additional considerations for cleaning of API production processes

1. Cleaning validation is a requirement to minimize cross contamination requirements in the production of APIs. Per risk management requirements, such activities should be focused on process steps that pose the greatest risk to product quality (i.e. later stage intermediates and final processing/handling stages).

2. In general, cleaning control and evaluation requirements for the final API production processes should be equivalent to those required for finished dosage form manufacture. For example:

    a. Relevant cleaning processes should be validated in accordance with a lifecycle approach.
    b. Equipment should be designed in accordance with the same concepts as used for finished drug products.
    c. Controls with respect to manufacturing and cleaning requirements should also be equivalent to finished drug requirements (e.g. room classification and quality of rinse water used).

3. API cleaning processes normally involve significant use of solvents. In such cases:

    a. Ensure the API is soluble in the agent being used for cleaning and rinse recovery studies.
    b. Ensure the solvents used for the cleaning process, including the final rinse, are of appropriate quality.
    c. Reflux or boil-out steps may be important when cleaning reactors and similar equipment to ensure appropriate solvent contact with the entire product contact equipment surface area. A reflux or boil-out step should also be included when collecting a rinse sample for qualification, verification, or monitoring activities.

4. Determine the need for residual solvent limits via QRM principles. You may find information on establishing limits for residual solvents in ICH Q3C: Impurities: Guideline for Residual Solvents.

14. Additional considerations for cleaning validation of biotechnology processes

1. The principles outlined in this document can generally be applied to the cleaning validation of biotechnology processes as well.

2. Cleaning development programs need to consider the cleaning of a large number of substances (e.g. media, proteins, acids, basses, salts, etc.)

3. Biotechnology cleaning processes often involve causing protein molecules to degrade:

a. There should be an understanding of the controls and parameters required for such degradation. Laboratory scale trials, therefore, take increased importance.

b. Residual measurements are normally performed using a non-specific test method such as TOC.

4. Cleaning validation requirements for biological drugs will normally include a microbiological and endotoxin assessment.

5. For biological drugs (including vaccines), you may use bracketing for similar products and/or equipment, provided there is appropriate justification (based on sound and scientific rationale).

Some examples include:

- Cleaning of fermenters of the same design, used for the same type of recombinant proteins expressed in the same rodent cell line and cultivated in closed related growth media.
- For multi-antigen vaccine used to represent the individual antigen (or other combinations of them) when validating the same or similar equipment that is used at stages of formulation (adsorption) and/or holding.

6. Validation of the cleaning product-contact equipment (such as fermenters) should be performed on a specific organism basis.

7. Biotechnology cleaning processes often cause the active molecule to change or degrade.

8. Due to degradation issues, the use of specific analytical testing methods may not be appropriate. Non-specific methods such as TOC will, therefore, sometimes be used.

Bulk Manufacture: Carryover calculations are typically not applicable for bulk manufacture.

- Limits in such cases are generally based on process capability.

- Calculations may also be based on toxicity values. In such cases, the relevant toxicity data is not the toxicity of the protein in question, but of the degraded fragments, which is often assumed to be less of a safety concern (but such studies are normally not performed).
- As a general rule, the limits may be more stringent following the purification.

Formulation and Final Filling: Limits are calculated based on a MACO that has been established from a toxicological assessment.

Appendices

Appendix A – Glossary

Acronyms

API:	Active pharmaceutical ingredient
CIP	Clean-in-place
GMP:	Good manufacturing practices
ICH:	International Council for Harmonisation
MACO:	Maximum Allowable Carry Over
PIC/S	Pharmaceutical Inspection Co-operation Scheme
QRM:	Quality Risk Management
TOC:	Total organic carbon

Terms

These definitions explain how terms are used in this document, as well as in the annexes (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.

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*)

In Division 1A and Division 2 of the Food and Drug Regulations, “drug” does not include a dilute drug premix, a medicated feed as defined in subsection 2(1) of the Feeds Regulations, 1983, an active ingredient that is for veterinary use and that is not an active pharmaceutical ingredient, 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 or a drug that is used only for the purposes of an experimental study in accordance with a certificate issued under section C.08.015. (C.01A.001(2))

Fabricate – “To prepare and preserve a drug for the purpose of sale.” (C.01A.001)

Potency – The activity or amount of active moiety, or any form thereof, indicated by label claim to be present.

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)

Appendix B – References

Laws and regulations

Food and Drugs Act
laws.justice.gc.ca/eng/acts/F-27/

Food and Drug Regulations
laws.justice.gc.ca/en/F-27/C.R.C.-C.870

International guidance documents

EMEA – Guideline on the Limits of Genotoxic Impurities (2006)
ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002903.pdf

FDA – Guide to Inspections of Validation of Cleaning Processes (1993)
https://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074922.htm

ICH – Impurities: Guideline for Residual Solvents Q3C (R6)
https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/notice-q3cr6.html

ICH – Quality Risk Management, Q9 (2016)
https://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

Parenteral Drug Association – Technical Report no. 29 (Revised 2012) "Points to Consider for Cleaning Validation"
https://store.pda.org/tableofcontents/tr2912_toc.pdf

Parenteral Drug Association – Technical Report No. 49 (Revised 2010) "Points to Consider for Biotechnology Cleaning Validation"
https://store.pda.org/tableofcontents/tr49_toc.pdf

Pharmaceutical Inspection Convention – Guide to Good Manufacturing Practice for Medicinal Product Annexes"
https://www.picscheme.org/en/publications?tri=gmp

Pharmaceutical Inspection Convention - Guide to good Manufacturing Practice for Medicinal Products Part I, Chapter 5
https://www.picscheme.org/en/publications?tri=gmp

Pharmaceutical Inspection Convention – Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation and Cleaning Validation (2007)
https://www.picscheme.org/en/publications?tri=gmp

VICH GL 18 – Residual solvents in new veterinary medicinal products, active substances and excipients (Revision)
hc-sc.gc.ca/dhp-mps/vet/legislation/guide-ld/vich/guide-ligne-eng.php

EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177735.pdf