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TO: ALL INTERESTED PARTIES

I am pleased to inform you that Health Canada has finalized the guidance document entitled “Cleaning Validation Guidelines (GUIDE-0028)”, which is now available on Health Canada’s Compliance and Enforcement website at:

http://www.hc-sc.gc.ca/dhp-mps/compli-conform/index_e.html

This document has been reviewed as part of the Inspectorate’s quality management process and has been amended to further clarify issues brought to the attention of the Inspectorate. Please note that no changes to the requirements were made, therefore, consultation is not deemed necessary.

Inquiries about this guidance document can be submitted in writing by mail to the Manager, Drug GMP Inspection Unit, HPFB Inspectorate, Graham Spry Building, A.L. #2002B, 250 Lanark Avenue, Ottawa, Ontario, K1A 0K9, by fax at 613 957-6709, or by e-mail at GMP_questions_BPF@hc-sc.gc.ca.

Original signed by

Diana Dowthwaite
Director General

OUR MANDATE:

To take an integrated approach to managing the health-related risks and benefits of health products and food by minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food, and promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

Health Products and Food Branch Inspectorate

Guidance Document

Cleaning Validation Guidelines

GUIDE-0028

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1.0 Scope

Disclaimer

This document does not constitute part of the Food and Drugs Act (Act) or the Food and Drugs Regulations (Regulations) and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies. This document is not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel.

This document on Cleaning Validation is intended to address special considerations and issues pertaining to validation of cleaning procedures for equipment used in the manufacture of pharmaceutical products, radiopharmaceuticals, and biological drugs. The document 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 in the preparation of this document.

The document is intended to cover validation of equipment cleaning for the removal of contaminants associated with previous products, residues of cleaning agents as well as the control of potential microbial contaminants.

2.0 Introduction

This document provides some guidance on issues and topics related to cleaning validation. This topic reflects an area in pharmaceutical, biological and radiopharmaceutical manufacturing that is noted as being important by both the Inspectorate and the pharmaceutical industry. This guideline has been prepared to provide guidance to inspectors, evaluators and industry in reviewing the issues covered. Utilization of this information should facilitate compliance with Division 2 Part C of the *Food and Drugs Regulations*.

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

3.0 Principles

3.1 The objective of the cleaning validation is to verify the effectiveness of the cleaning procedure for removal of product residues, degradation products, preservatives, excipients, and/or cleaning agents as well as the control of potential microbial contaminants. In addition one needs to ensure there is no risk associated with cross-contamination of active ingredients.

3.2 Cleaning procedures must strictly follow carefully established and validated methods.

3.3 Appropriate cleaning procedures must be developed for all product-contact equipment used in the production process. Consideration should also be given to non-contact parts into which product may migrate (e.g., seals, flanges, mixing shaft, fans of ovens, heating elements, etc.).

3.4 Relevant process equipment cleaning validation methods are required for biological drugs because of their inherent characteristics (proteins are sticky by nature), parenteral product purity requirements, the complexity of equipment, and the broad spectrum of materials which need to be cleaned.

3.5 Cleaning procedures for products and processes which are very similar do not need to be individually validated. This could be dependent on what is common, equipment and surface area, or an environment involving all product-contact equipment.

It is considered acceptable to select a representative range of similar products and processes. The physical similarities of the products, the formulation, the manner and quantity of use by the consumer, the nature of other product previously manufactured, the size of batch in comparison to previously manufactured product are critical issues that justify a validation program.

A single validation study under consideration of the worst case can then be carried out which takes account of the relevant criteria.

For biological drugs, including vaccines, bracketing may be considered acceptable for similar products and/or equipment provided appropriate justification, based on sound and scientific rationale, is given. Some examples are cleaning of fermenters of the same design but with different vessel capacity used for the same type of recombinant proteins expressed in the same rodent cell line and cultivated in closely related growth media; a 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. Validation of cleaning of fermenters should be done upon individual pathogen basis.

4.0 Validation of Cleaning Processes

4.1 As a general concept, until the validation of the cleaning procedure has been completed, the product contact equipment should be dedicated.

4.2 In a multi-product facility, the effort of validating the cleaning of a specific piece of equipment which has been exposed to a product and the cost of permanently dedicating the equipment to a single product should be considered.

4.3 Equipment cleaning validation may be performed concurrently with actual production steps during process development and clinical manufacturing. Validation programs should be continued through full scale commercial production.

4.4 It is usually not considered acceptable to test-until-clean. This concept involves cleaning, sampling, and testing with repetition of this sequence until an acceptable residue limit is attained.

4.5 Products which simulate the physicochemical properties of the substance to be removed may be considered for use instead of the substances themselves, when such substances are either toxic or hazardous.

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

4.7 All pertinent parameters should be checked to ensure the process as it will ultimately be run is validated. Therefore, if critical temperatures are needed to effect cleaning, then these should be verified. Any chemical agents added should be verified for type as well as quantity. Volumes of wash and rinse fluids, and velocity measurements for cleaning fluids should be measured as appropriate.

4.8 If automated procedures are utilized (Clean-In-Place: CIP), consideration should be given to monitoring the critical control points and the parameters with appropriate sensors and alarm points to ensure the process is highly controlled.

4.9 During a campaign (production of several batches of the same product), cleaning between batches may be reduced. The number of lots of the same product which could be manufactured before a complete/ full cleaning is done should be determined.

4.10 Validation of cleaning processes should be based on a worst-case scenario including:

(i) challenge of the cleaning process to show that the challenge soil can be recovered in sufficient quantity or demonstrate log removal to ensure that the cleaning process is indeed removing the soil to the required level, and

(ii) the use of reduced cleaning parameters such as overloading of contaminants, over drying of equipment surfaces, minimal concentration of cleaning agents, and/or minimum contact time of detergents.

4.11 At least three (3) consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated. Equipment which is similar in design and function may be grouped and a worst case established for validation.

5.0 Equipment and Personnel

Equipment:

5.1 All processing equipment should be specifically designed to facilitate cleanability and permit visual inspection and whenever possible, the equipment should be made of smooth surfaces of non-reactive materials.

5.2 Critical areas (i.e., those hardest to clean) should be identified, particularly in large systems that employ semi-automatic or fully automatic CIP systems.

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

5.4 In a bulk process, particularly for very potent chemicals such as some steroids, the issue of by-products needs to be considered if equipment is not dedicated.

Personnel:

5.5 It is difficult to validate a manual cleaning procedure (i.e. an inherently variable/cleaning procedure). Therefore, operators carrying out manual cleaning procedures should be adequately trained, monitored, and periodically assessed.

6.0 Microbiological Considerations

6.1 Whether or not CIP systems are used for cleaning of processing equipment, microbiological aspects of equipment cleaning should be considered. This consists largely of preventive measures rather than removal of contamination once it has occurred.

6.2 There should be some documented evidence that routine cleaning and storage of equipment do not allow microbial proliferation. For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations. Time-frames for the storage of unclean equipment, prior to commencement of cleaning, as well as time frames and conditions for the storage of cleaned equipment should be established.

6.3 The control of the bio-burden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility. This is also particularly important from the standpoint of the control of pyrogens in sterile processing since equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

7.0 Documentation

7.1 Detailed cleaning procedure(s) are to be documented in SOPs

7.2 A Cleaning Validation Protocol is required to define how the cleaning process will be validated. It should include the following:

- The objective of the validation process;
- Responsibilities for performing and approving the validation study;
- Description of the equipment to be used;
- The interval between the end of production and the beginning of the cleaning procedure;
- The number of lots of the same product, which could be manufactured during a campaign before a full cleaning is done
- Detailed cleaning procedures to be used for each product, each manufacturing system or each piece of equipment;
- The number of cleaning cycles to be performed consecutively;
- Any routine monitoring requirement;
- Sampling procedures, including the rationale for why a certain sampling method is used;
- Clearly defined sampling locations;
- Data on recovery studies where appropriate;
- Validated analytical methods including the limit of detection and the limit of quantitation of those methods;
- The acceptance criteria, including the rationale for setting the specific limits;
- Other products, processes, and equipment for which the planned validation is valid according to a “bracketing” concept;
- Change Control/ Re-validation.

7.3 Depending upon the complexity of the system and cleaning processes, the amount of documentation necessary for executing various cleaning steps or procedures may vary.

7.4 When more complex cleaning procedures are required, it is important to document the critical cleaning steps. In this regard, specific documentation on the equipment itself which includes information about who cleaned it, when the cleaning was carried out, the product which was previously processed on the equipment being cleaned should be available. However, for relatively simple cleaning operations, the mere documentation that the overall cleaning process was performed might be sufficient.

7.5 Other factors such as history of cleaning, residue levels found after cleaning, and variability of test results may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and of the operator performance. Appropriate evaluations must be made, and when operator performance is deemed a problem, more extensive documentation (guidance) and training may be required.

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

8.0 Analytical Methods

8.1 The analytical methods used to detect residuals or contaminants should be specific for the substance or the class of substances to be assayed (e.g., product residue, detergent residue, and/or endotoxin) and be validated before the cleaning validation study is carried out.

8.2 If levels of contamination or residual are not detected, it does not mean that there is no residual contaminant present after cleaning. It only means that the levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample.

8.3 In the case of biological drugs, the use of product-specific assay(s) such as immunoassay(s) to monitor the presence of biological carry-over may not be adequate, a negative test may be the result of denaturation of protein epitope(s). Product-specific assay(s) can be used in addition to total organic carbon (TOC) for the detection of protein residue.

8.4 The analytical method and the percent recovery of contaminants should be challenged in combination with the sampling method(s) used (see below). This is to show that contaminants can be recovered from the equipment surface and to show the level of recovery as well as the consistency of recovery. This is necessary before any conclusions can be made based on the sample results. A negative test may also be the result of poor sampling technique.

9.0 Sampling, Rinsing, Rinse Samples and Detergents

Sampling:

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

9.2 Direct Surface Sampling

(I) Areas hardest to clean and which are reasonably accessible can be evaluated by direct sampling method, leading to establishing a level of contamination or residue per given surface area.

Additionally, residues that are "dried out" or are insoluble can be sampled by physical removal.

(ii) The suitability of the material to be used for sampling and of the sampling medium should be determined. The ability to recover a sample accurately may be affected by the choice of sampling material. It is important to assure that the sampling medium and solvent (used for extraction from the medium) are satisfactory and can be readily used.

9.3 Rinse Samples

(I) Rinse samples allow sampling of a large surface area and of inaccessible systems or ones that cannot be routinely disassembled. However consideration should be given to the fact that the residue or contaminant may be insoluble or may be physically occluded in the equipment.

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

9.4 Indirect testing such as conductivity and TOC testing may be of some value for routine monitoring once a cleaning process has been validated. This could be applicable to reactors or centrifuge and piping between such large equipment can be sampled only using rinse solution samples.

9.5 If the placebo method is used to validate the cleaning process then it should be used in conjunction with rinse and/or swab samples. It is difficult to provide assurance that the contaminate will be uniformly dispersed throughout the system or that it would be worn off the equipment surface uniformly. Additionally, if the contaminant or residue is of large enough particle size, it may not be uniformly dispersed in the placebo. Finally, the analytical power of the assay may be greatly reduced by dilution of the contaminant.

9.6 It is important to use visual inspection in addition to analytical methodology to ensure the process is acceptable.

Detergents:

9.7 When detergents are used in the cleaning process, their composition should be known to the user and their removal should be demonstrated. The manufacturer should ensure that they are notified by the detergent supplier of any changes in the formulation of the detergent.

9.8 Detergents should be easily removable, being used to facilitate the cleaning during the cleaning process. Acceptable limits should be defined for detergent residues after cleaning. The possibility of detergent breakdown should also be considered when validating cleaning procedures.

Last Rinse:

9.9 Water for injection should be used as the last rinse for product-contact equipment to be utilized in the fabrication of sterile products.

9.10 Purified water is considered acceptable as the last rinse for product-contact equipment used in the fabrication of non-sterile products or sterile products for ophthalmic use.

Note: Because of the presence of varying levels of organic and inorganic residues as well as of chlorine, tap water should not be used in the last rinse of any cleaning procedure for product-contact equipment.

10.0 Establishment of Limits

10.1 The fabricator's rationale for selecting limits for product residues should be logical and based on the materials involved and their therapeutic dose. The limits should be practical, achievable, and verifiable.

10.2 In establishing product residual limits, it may not be adequate to focus only on the main reactant since by-products/chemical variations (active decomposition material) may be more difficult to remove. In addition to chemical testing, Thin Layer chromatography screening may be needed in certain circumstances.

10.3 The approach for setting limits can be:

- (1) product specific cleaning validation for all products;
- (2) grouping into product families and choosing a worst case product;
- (3) grouping by properties (e.g., solubility, potency, toxicity or formulation ingredients known to be difficult to clean);
- (4) setting limits on not allowing more than a certain fraction of carryover;
- (5) different safety factors for different dosage forms.

10.4 Carry-over of product residues should meet defined criteria for example the most stringent of the following criteria (I, ii, iii):

- (I) NMT 0.1% of the normal therapeutic dose of any product to appear in the maximum daily dose of the following product;
- (ii) NMT 10 ppm of any product to appear in another product;
- (iii) No quantity of residue to be visible on the equipment after cleaning procedures are performed. Spiking studies should determine the concentration at which most active ingredients are visible.
- (iv) For certain highly sensitizing or highly potent ingredients (such as penicillins, cephalosporins or potent steroids and cytotoxics), the limits should be below the limit of detection by best available analytical methods. In practice this may mean that dedicated plants are used for these products.

11.0 Change Control/Revalidation

11.1 A change control system is in place to ensure that all changes that might impact the cleaning process are assessed and documented. Significant changes should follow satisfactory review and authorization of the documented change proposal through the change control procedure. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system. The review should include consideration of re-validation of the cleaning procedure.

11.2 Changes which should require evaluation and likely re-validation include but not limited to:

- Changes in the cleaning procedure;
- Changes in the raw material sources;
- Changes in the formulation and/or process of products;
- New products;
- Changes in the formulation of detergents;
- New detergents;
- Modifications of equipment.

11.3 The cleaning process should be reassessed at defined intervals, and re-validated as necessary. Manual methods should be reassessed at more frequent intervals than clean-in-place (CIP) systems.

12.0 References

1. FDA, Guide to Inspections of Validation of Cleaning Processes, 1993.
2. Pharmaceutical Inspection Convention, Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation and Cleaning Validation, 2004.