Corp Validation Plan

Cleaning Validation Plan

Version 2

Effective Date:

Version	Effective Date	Change Description
2		

CLEANING VALIDATION PLAN

VP2011-03

Revision 2

Aphena Pharma Solutions

APPROVALS

By affixing their signatures, the individuals below agree that they have reviewed and approved the scope of the effort described in this Cleaning Validation Plan for Aphena Pharma Solutions. The signatures below represent the approval for execution of the Cleaning Validation Plan and acceptance by Aphena Pharma Solutions authorized signatories.

Name / Title	Signature	Date
Gregory Lane VP Quality and Regulatory Affairs	/s/ Gregory Lane /s/	8/16/2018
Name / Title	**Signature**	**Date**
Bob Scott President Solid Dose Division	/s/ Bob Scott /s/	8/15/2018
Robert Maddox President Liquids Division	/s/ Robert Maddox /s/	8/15/2018
Chris Campbell Director of Quality & Regulatory Affairs Solid Dose Division	/s/ Chris Campbell /s/	8/15/2018
Patrice Hambleton Director of Quality & Regulatory Affairs Liquids Division	/s/ Patrice Hambleton /s/	8/15/2018

REVISION HISTORY

Revision #	Date	Name	Reason for Change
Aphena Pharma Solutions Cleaning Validation Plan, Revision 0	01Jan2012	Mary Foster	Initial creation of corporate- wide Cleaning Validation Plan. Replaces CVMP2011-001 for the Easton facility.
Rev 1	08/29/2016	Gregory Lane	Periodic review
Rev 2	7/31/2018	Gregory Lane	Remove address reference and update approvers

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1. INTRODUCTION

This Cleaning Validation Plan (CVP) defines the Aphena Pharma Solutions (Aphena) approach for assuring that cleaning validation requirements for product contact surfaces of packaging and manufacturing equipment are met, studies are completed as appropriate, and an ongoing system of review is maintained to keep the cleaning validation status current. Implementation of this plan will assure compliance with regulatory and customer requirements for cleaning validation.

2. SCOPE

This CVP applies to cleaning processes for product-contact surfaces of packaging and manufacturing equipment located at all Aphena Pharma Solutions facilities. Products at these facilities may be contract packaged and/or manufactured for sponsors, or they may be Aphena's formulations. This CVP is a tier II document under Aphena's Master Validation Plan, VMP2011-01.

This CVP applies to cleaning procedures for equipment product-contact surfaces for all stages of Good Manufacturing Practice (GMP) packaging and manufacturing processes where the potential for cross-contamination exists. Once product is in its primary package, cleaning validation is not required.

Some of the products packaged and/or manufactured by Aphena are medical devices and some are personal care/cosmetic products. Such non-drug products are included in this CVP provided the potential exists for cross-contamination of the non-drug product into drug products or for the cross contamination of the drug products into the non-drug products.

This CVP shall be used for all new change controls initiated after the effective date of this plan.

2.1 Facilities

The equipment/systems required to manufacture products at the facilities have been designed to operate in compliance with current GMP regulations, as required by the US Food and Drug Administration (FDA). These requirements include cleaning validation.

2.2 Cleaning Process Description

Following manufacture of a product on product contact equipment, Aphena performs a cleaning process. These processes may be manual cleaning process, semi-automated, or fully automated cleaning processes. This cleaning process is the critical cleaning step that requires measurement of residues as part of a cleaning validation or verification protocol.

2.3 Assumptions and Exclusions

The following Assumptions and Exclusions have been taken into consideration in preparing this CVP:

- Test Instruments used in the performance of the validation activities will be calibrated and will have a current certificate of calibration from a recognized source consistent with the provisions of Aphena Master Validation Plan MVP2011-001.
- Cleaning validation is not required for secondary packaging processes because product is not exposed to equipment surfaces.
- Aphena does not process highly hazardous actives, such as actives that are mutagenic, teratogenic, and cytotoxic. Therefore, concerns for such actives are not applicable to this CVP. If Aphena were to process these materials, this CVP will be reviewed for any required modifications.
- Equipment used for cleaning in cleaning validation protocols will already have IQ and OQ performed and approved.

2.4 Training

All those performing any validation activities will be trained on the current Work Instructions (WIs) and Standard Operating Procedures (SOPs) relevant to the cleaning validation project using applicable personnel qualifications and training policies for the facility. This includes training on cleaning procedures, sampling procedures and analytical procedures.

3. RESPONSIBILITIES

- Quality prepares and approves validation protocols
- Operations and Project Management review and approve validation protocols
- Quality and operations coordinate execution of validation protocols
- Quality prepares the final report for each validation protocol
- Quality selects sampling sites and sampling methods for equipment
- Quality determines residue limits for validation protocols
- Quality collects samples during protocol execution
- Operations and Quality perform visual inspection of equipment following cleaning in a protocol
- Quality maintains the validation status summary report
- Quality performs and documents yearly cleaning validation review
- Operations develops and writes cleaning procedures
- Operations executes the cleaning procedure in protocols

- Operations and Quality investigate and resolve protocol deviations
- Quality releases equipment for use based on the protocol results
- Quality analyzes active and cleaning agent samples in protocols
- Quality analyzes bioburden samples in protocols
- Quality validates analytical methods, including determining sampling recoveries
- Quality prepares the final report for each validation protocol
- Quality and Operations coordinate yearly confirmatory runs for representative manual cleaning processes

4. CLEANING VALIDATION DOCUMENTATION PRACTICES

All executed forms must be filled out and/or completed in accordance with established site procedures for documentation practices.

5. GENERAL CLEANING VALIDATION APPROACH

Below is a list of steps for how to plan, execute and report cleaning validation.

- Determine the requirements for cleaning validation for a new product. The decision tree in Appendix D may be utilized to assist in this determination.
- Define system to be cleaned, including equipment, manufactured products, potential contaminants, and potential subsequent products
- Design and develop the cleaning procedure, including critical process control parameters
- Design overall cleaning validation approach, including any grouping strategy, residues to be measured, acceptance limits for residues, sampling methods, and sampling locations
- Develop and validate analytical methods to be employed
- Perform recovery studies on applicable surface materials
- Prepare and approve cleaning validation protocol
- Execute cleaning validation protocol

- Write and approve final report
- Maintain validated state as stated in protocol and/or as revised by change control and periodic review

6. DESIGN OF CLEANING PROCEDURES

Cleaning documentation shall have adequate detail to provide appropriate consistency of execution for the method. Adequate detail may include information to control parameters such as detergent concentration, temperature, time and manual cleaning actions, as well as sequence of process steps. Adequate control also includes specification of detergent and cleaning tools (such as brushes or wipes).

6.1 Design and development of a cleaning process for a new product and/or new equipment shall be documented in a technical report. That technical report may include laboratory studies, scale-up studies, and/or references to cleaning processes for sufficiently similar cleaning situations. The technical report shall include the objective, the product(s) being cleaned, the equipment use for packaging and/or manufacture, a summary of all relevant studies including references to reports and/or data for those studies, a summary of any relevant cleaning WIs for may be applicable to this new cleaning situation, a conclusion as to the recommended cleaning procedure, and a discussion of critical process parameters for the cleaning procedure,

6.2 For automated cleaning processes, consistency may be established by PLC control of cleaning parameters. For manual cleaning processes, consistency may be controlled by adequate specification of actions in the written cleaning procedure and by training of operators.

6.3 Procedures may be written for specific equipment or for groups of equipment. Procedures may be specific to one manufactured product or may apply to a group of manufactured products on the same equipment and/or equipment group.

7. SPECIAL CLEANING SITUATIONS

7.1 Dedicated equipment is defined as equipment used exclusively for a single product. For dedicated equipment, visual inspection alone may be used as the acceptance criterion for any active ingredient. However, cleaning validation/verification is required to establish that residues of cleaning agent/detergent and bioburden are acceptable, as well as to establish that the equipment is visually clean.

7.2 Between lots of the same liquid formulations, a water or organic solvent flush may be performed to remove gross residues from equipment surfaces. Between lots of the same solid formulations, a vacuuming may be performed to remove gross residues from equipment surfaces. Such “minor” cleaning does not require validation. However, “minor” cleaning shall be considered when establishing criteria for the maximum number of product lots to be manufactured before a validated cleaning process is to be used.

7.3 For cleaning following intrusive maintenance on equipment, such equipment may be first cleaned with a cleaning process suitable for the intrusive maintenance. However, prior to return to service the equipment shall be cleaned with an approved, validated cleaning process for such equipment. In such cases involving the final use of a validated cleaning process, no sampling or analysis following final cleaning shall be required.

8. CLEANING VALIDATION STRATEGIES

Cleaning validation may involve separate protocols for each combination of product and equipment, or may involve grouping approaches for products, for equipment, and for combinations of products and equipment. Any approach may be utilized, and may include some products on a given equipment item validated separately while other products on that same equipment item are validated based on a grouping approach. The approach used must be specified in the protocol.

8.1 Single-Use Equipment

Certain product-contact equipment is used once and then discarded. Single use items shall be cleaned as appropriate for safe disposal, but shall be excluded from those items for which residue limits are established and measured in cleaning validation protocols.

8.2 Product Grouping

Product grouping may be used when different products are manufactured on the same or equivalent equipment and when all products in the group are cleaned by the same cleaning procedure. Validation is performed by performing a validation protocol on the worst-case (most difficult to clean) product, with the acceptance criterion of the active established at the lowest limit of any active in the product group. The rationale for the selection of the worst-case product shall be specified or referenced in the associated cleaning validation protocol. Successful validation of the worst-case product shall mean that cleaning validation for all other products in the group is established. Because of the applicability of the validated cleaning procedure to multiple products, the protocol shall require a minimum of three validation runs on the worst-case product for successful validation of a product group.

8.2.1 **Addition of a new product to an established group**

If a new product is added to a previously established, validated product group, the new product shall be evaluated using the same criteria previously used to establish the worst-case product.

If the new product is not a new worst-case product, then a determination shall be made whether addition of the new product results in a new "lowest limit of any product in the group". If a new lowest limit is found, then the group shall be validated again using the worst-case product and the new lowest limit. If a new lowest limit is not found, then a confirmatory validation run shall be performed on the initial manufacture/packaging of the product, with the sole acceptance criterion being that the equipment is visually clean. If the confirmatory run is acceptable, then the cleaning validation of the new product shall be successfully established.

If the new product is a new worst case, the effect of the new product on the lowest limit of the previously validated group shall be determined. If the new product does not change the lowest limit for the established group, then either (a) a new group is established and validation is established using the criteria in Section 8.2, or (b) cleaning validation is established separately for the new product apart from the previously grouped products. If the new product results in a new lowest limit for the previously established group, then a new group is established and validation for the new group shall be established using the criteria in Section 8.2.

8.2.2 Grouping across facilities

For relatively straightforward cleaning procedures, such as manual cleaning of tablet/capsule packaging equipment in a central cleaning area, the grouping approach for cleaning validation may be applied among different facilities provided the cleaning procedures of the facilities are substantially identical and provided the operator training programs for the cleaning process of the facilities are substantially equivalent. In such a grouping approach across faculties, the approach at a minimum shall be to conduct three (3) validations runs on a worst-case product at one facility to validate the cleaning process, and one (1) confirmatory run at each other facility to establish applicability of that validated procedure to that other facility. If this approach is used for a manual cleaning process, a yearly confirmatory validation run as specified in Section 17.5 shall be performed in each facility on that cleaning process.

8.3 Equipment Grouping

Equipment grouping may be used when identical or similar equipment is cleaned after manufacturing the same product using the same cleaning procedure. Equipment identical by IQ and OQ may be validated as a group, with the validation protocol being performed on any combination of the identical items. For similar equipment items, the protocol runs shall be performed on the most difficult to clean of the similar equipment items. If the most difficult to clean cannot be clearly established, then three validation runs shall be performed including at least one run at the extremes of equipment variation (for example, storage tanks of different sizes). If there are no relevant extremes of similar equipment, then validation runs shall be performed on any combination of similar equipment items. Because of the applicability of the validated cleaning procedure to multiple equipment items, the protocol shall require a minimum of three validation runs for identical or similar equipment.

8.3.1 Addition of a new equipment item to an established group

If a new *identical* equipment item is to be added to an already validated equipment group, then a confirmatory validation run should be performed on the initial manufacture of the product using the new equipment item, with the sole acceptance criterion being that the equipment is visually clean. If the confirmatory run is acceptable, then the cleaning validation of the new equipment item with the applicable product(s) and cleaning process shall be successfully established.
If a new similar equipment item is to be added to an already validated equipment group and the new equipment items does not constitute a most difficult to clean equipment item in the group, nor constitute a new extreme of equipment variation, then a confirmatory validation run should be performed on the initial manufacture of the product in the new equipment item, with the sole acceptance criterion being that the equipment is visually clean. If the confirmatory run is acceptable, then the cleaning validation of the new equipment item with the applicable product(s) and cleaning process shall be successfully established.

If the new similar equipment item constitutes a most difficult to clean equipment item in the group, then either cleaning validation shall be performed for the new group using the criteria in Section 8.2, or that equipment item shall be validated separately.

If the new similar equipment item constitutes a new extreme of equipment variation, then a confirmatory validation run should be performed on the initial manufacture of the product in the new equipment item, with the residue acceptance criteria calculated as in the original validation of the items in the group. If the confirmatory validation run is acceptable, then the cleaning validation of the new equipment item with the applicable product(s) and cleaning process shall be successfully established.

8.4 Combined Product and Equipment Grouping

Both product grouping and equipment grouping may be combined together as a grouping approach provided the criteria of both Section 8.2 and Section 8.3 are met.

8.5 Grouping Documentation

In all cases involving grouping, the grouping rationale shall be given in a separate document that is referenced in the validation protocol.

9. RESIDUES AND ACCEPTANCE LIMITS IN PROTOCOLS

All products manufactured in the Aphena Easton facility are non-sterile preparations. Therefore, residues to be measured in cleaning validation protocols are the drug active, the cleaning agent (detergent), and bioburden. If Aphena is aware of any significant degradation products which might be a cross-contamination issue, an evaluation should be made as to whether acceptance limits in protocols should be established for those degradation products. In addition, a general evaluation of cleanliness shall be made by confirming that the equipment is visually clean.

9.1 Limits for Actives in Liquid and Solid Oral Dosage Products

For liquid and solid oral dosage products, the residue acceptance criterion for the active shall be such that no more than 0.001 (one one-thousandth) of the minimum dose of the active of the cleaned product shall appear in a maximum dose of the subsequently manufactured product. Formulas for calculating this limit are given in Appendix A. In any validation protocol, a default residue limit for the active ingredient may be utilized provided that such default value is less than that limit calculated using Attachment A. Aphena shall utilize a default limit of 10 ppm of the active in the subsequently manufactured product.

9.2 Limits for Actives in Topical Dosage Forms

For topical dosage forms (which may be creams, ointments, or liquids), the residue acceptance criterion for the active shall be such that no more than 0.001 (one one-thousandth) of the minimum dose of the active of the cleaned product shall appear in a maximum dose of the subsequently manufactured. Formulas for calculating this limit are given in Appendix B. In any validation protocol, a default residue limit for the active ingredient may be utilized provided that such default value is more stringent than that limit calculated using Appendix A. Aphena shall utilize a default limit of 10 ppm of the active in the subsequently manufactured product.

9.3 Limits for Products with Multiple Actives

If a product contains more than one active, limits are only required to be established and residues measured in protocols for the active with the lowest solubility. In such a case, the residue limit for that active shall be the lowest limit of any active in the product. If such an approach is not practical, then limits shall be established and measured in protocols for each active separately

9.4 Limits for Bioburden

For sampling using swabs, a bioburden acceptance criterion for total aerobic bacteria shall be no more than 2 CFU/cm^2 of sampled area. For sampling using rinse water, a bioburden acceptance criterion for total aerobic bacteria shall be no more than a total of 100 CFU/mL (the typical acceptance criterion for USP Purified Water). These criteria are based on standard industry practice, and are well below what would constitute product adulteration by bioburden. Furthermore, no USP objectionable organisms shall be present as bioburden on cleaned product contact surfaces.

9.5 Limits for Cleaning Agents/Detergents

The residue acceptance criterion for the cleaning agent/detergent shall be such that no more than an oral Acceptable Daily Intake (ADI) shall appear in the maximum daily dose of the subsequently manufactured product. Formulas for calculating this limit are given in Appendix C. While this oral ADI criterion is directly applicable for orally dosed products, it is a conservative approach for topically applied products. In any validation protocol, a default residue limit for the cleaning agent/detergent may be utilized provided that such default value is more stringent than that limit calculated using Appendix C. Aphena shall

utilize a default limit of 10 ppm of the cleaning agent/detergent solids in the subsequently manufactured product.

9.6 Limits for Volatile Organic Solvents

Where a volatile organic solvent (such as isopropanol) is used as a final rinse or treatment for equipment surfaces, it is not required that limits be established for that volatile solvent provided either that adequate conditions exist for that solvent to evaporate from surfaces following treatment or that solvent is used in the formulation of the subsequent product.

9.7 Overall Cleanliness Evaluation

Following the cleaning process, the dry product-contact surfaces shall be visually observed, and shall be visually clean of any manufactured product and cleaning agent/detergent. Normal product-contact part surface blemishes and variations shall not constitute failure under this criterion. Such normal blemishes and variations shall be documented in the cleaning protocol before execution of the manufacturing process for the cleaning validation run.

9.8 Visually Clean as the Most Stringent Acceptance Criterion

A visually clean criterion may be used as the acceptance criterion for an active and/or a cleaning agent provided that such a criterion is more stringent than the surface area limit calculated for that active or cleaning agent. Such stringency shall be demonstrated by laboratory spiking studies of the residue on coupons at levels above the surface area limit calculation value, following by observing those coupons under conditions the same or more stringent than the viewing conditions on production equipment during protocol execution. More stringent viewing conditions shall mean a shorter distance and/or brighter lighting. If the residue is visible across the entire spiked surface of the coupon in the laboratory evaluation, then any surface viewed under the same conditions which is visually clean shall have been demonstrated to have residues values below the spiked surface level.

9.9 Degradation Products

Degradation products may be a potential issue for active ingredients that are degraded by the cleaning solution and cleaning parameters. If degradation products pose a significant risk for the product subsequently manufactured, they should be addressed in the cleaning validation protocol. The toxicity and solubility of the degradation products could serve as guidance for what evaluation is needed. In cases where the active ingredient is completely degraded due to the cleaning process, if the safety concern of the degradants is not greater than the safety concerns of the active ingredient, limits can be established based on a carryover calculation of the active ingredient, with use of TOC as a worst-case analytical method to measure residues.

10. SAMPLING METHODS

Swab and/or rinse sampling may be used as appropriate for the equipment sampled in order to analytically measure residue on surfaces.

10.1 Swab Sampling

Swabs for chemical residues may be used dry or saturated with a suitable solvent to aid in the solubility and physical removal of surface residues. The specific swab used, the wetting solution (if any) for the swab, and the number of swabs used per location should be specified in the cleaning validation protocol. Swabs for microbiological residues are typically sterile cotton swabs, which are wetted with Letheen Broth. Only one swab is used per location for microbiological sampling. The configuration and complexity of the equipment will determine the number of swab sample sites for that equipment. The sites selected for swabbing shall include equipment surfaces which are most difficult to clean (hard to clean) and surfaces which represent a potential non-uniform transfer to the next manufactured batch (such as filling needles), and may also include representative materials of construction and representative functional locations on the equipment. The number and location of sample sites shall be specified in the cleaning validation protocol.

The standard swabbed area for Aphena shall be four inches by four inches (sixteen square inches). A standard swabbed area assures more consistency in training in the swabbing process. However, if the equipment location sampled requires a slightly larger or smaller sampled area (4 square inches to 24 square inches), then that swabbed area should be specified for that location, and the residue limit for that location adjusted accordingly.

10.2 Rinse Sampling

Rinse sampling is sampling a specified surface, usually the entire equipment product contact surface, with a known volume of diluent. The diluent is subsequently collected and tested for the presence and quantification of residues for which acceptance limits are set. Rinse sampling may involve a grab sample of a final process rinse (as in a CIP process rinse) or a separate sampling rinse. Rinse sampling is the preferred sampling method for measuring residues of readily rinseable detergents.

11. ANALYTICAL METHODS AND THEIR VALIDATION

11.1 Test Methods for Actives and Cleaning Agents

For residues of actives in finished drug products and for residues of detergents, validated analytical methods shall be used to measure residues for which an acceptance limit is established.

11.1.1 Methods may be either specific for the residue or may be non-specific, provided the non-specific method is a direct measure of the target residue. For non-specific methods, the measured non-specific response shall be handled as if all of the response is due to the target residue.

11.1.2 Methods for cleaning agents may be specific for a component in the detergent (such as the surfactant), or may be non-specific for a general property of the cleaning agent (such as conductivity).

11.1.3 Methods shall be validated using the principles of ICH Q2 (R1). Applicable compendia methods, such as USP or AOAC methods, do not require validation, but suitability for use shall be established. When using non-specific methods, the method should be validated or suitability for use established for a specific residue.

11.1.4 Analytical methods shall be validated for linearity at the residue limit in the analytical sample down to at least 50%, and preferably 10%, of that residue limit.

11.1.5 Analytical methods may involve pass/fail tests, where the analytical method solely determines whether the sample is below the acceptance limit. Such tests allow more limited method validation consistent with ICH Q2 (R1). Such pass/fail methods, if used, are more likely to be used for non-drug products and/or for cleaning verification purposes.

11.2 Test Methods for Bioburden

Microbiological procedures for bioburden shall be by approved microbiology laboratory procedures. Microbiological methods for bioburden that are approved microbiology laboratory procedures do not require further validation.

12. SAMPLING RECOVERY STUDIES

Laboratory recovery studies shall be performed for appropriate combinations of chemical analytical method, sampling procedure, and surface type for residues of the active ingredient and the detergent.

12.1 A surface type which constitutes less than 1% of the total equipment shared surface area for manufacture shall not require a recovery study. In such a case, a default recovery value of 50% shall be used for such surface comprising less than 1% of the total surface area.

12.2 For swab sampling, recovery studies shall involve a minimum of six replicates. If only one operator is involved, three replicates should be done on one day and three replicates on another day. For rinse sampling, which is not operator dependent, recovery studies only require three replicates by one operator.

12.3 The recovery percentage for a given chemical residue and surface type shall be determined as the lowest mean recovery percentage of any operator.

12.4 Recovery percentages greater than or equal to 50% shall be utilized without additional justification. Recoveries of less than 50% may be utilized only with a written justification.

12.5 For swabbing, recovery percentages shall be performed on a nominal 16 square inches surface area, and shall be applicable to all sampling areas from 4 square inches to 24 square inches. For rinse sampling, recovery studies shall be performed on a nominal 16 square inches surface area and shall apply to rinsing of any surface area.

12.6 Recovery percentages shall be utilized to adjust the measured residue in the analytical sample. Adjustment is accomplished by dividing the measured analytical value by the recovery percentage expressed as a decimal. The corrected analytical value is then compared to the calculated limit.

12.7 Recovery studies and recovery percentages are not appropriate for and are not required for bioburden sampling.

13. CLEANING VALIDATION PROTOCOLS

For cleaning validation, an approved validation protocol shall be used which specifies applicable validation parameters, including the cleaning process utilized, the applicable process equipment covered by the protocol, the applicable product or products covered by the protocol, the specific representative equipment and/or product if a grouping approach is utilized, challenges to the cleaning process, sampling methods and locations, analytical methods utilized, predetermined acceptance criteria, and proposed ongoing maintenance of the validated state. For cleaning validation, such protocols shall ordinarily be utilized in place of a separate Project Validation Plan (PVP).

13.1 The number of validation runs for a protocol shall ordinarily be three runs, unless there is a valid rationale for a different number of runs (either more than three or fewer than three). Such rationale shall be given or referenced in the validation protocol.

13.2 Challenges to the cleaning process during protocol execution may include “worst case” conditions within normal processing parameters. If a worst case condition or source of variation is adequately addressed in the cleaning process design and development, it is not required to include that challenge in the cleaning validation protocol.

13.3 During protocol execution, deviations to either the cleaning process or the protocol execution shall be resolved using an approved deviation investigation and resolution procedure. Such deviations for a protocol run shall be evaluated as to whether the deviation would cause the analytical results to be invalid.

13.4 Following execution of individual runs in a protocol, an interim validation report may be written. Following execution of all validation runs in a protocol, a final report shall be prepared summarizing the performance and results of all runs in the validation protocol. Such a report shall also summarize any deviations to the cleaning process and/or protocol execution. Based on the documented evidence, such report shall clearly state whether the applicable cleaning process is validated.

13.5 After visual examination and sampling in protocol execution, an evaluation shall be made as to whether the equipment has been compromised by the sampling procedure. If so, the equipment shall be cleaned again by the same cleaning procedure, without any additional testing except that the equipment be visually clean.

13.6 During protocol execution for each validation run, equipment may be released by Quality for use by Operations provided all acceptance criteria are met and provided any deviations were found not to affect analytical results.

13.7 Products packaged and/or manufactured either before or after a cleaning validation run shall be released using Aphena's product release criteria. If either product is also undergoing process validation, criteria for release of that product shall be as specified in the process validation protocol.

14. CLEANING VERIFICATION PROTOCOLS

For products made infrequently (such as an initial batch for customer sampling purposes), for initial cleaning of new equipment, for cleaning following equipment maintenance, and/or for cleaning following deviations, a cleaning verification approach may be used. Cleaning verification involves setting limits and measuring residues for a one-time cleaning event. Cleaning verification ensures that the equipment is clean by appropriate testing, but this is not considered a validated cleaning process. Validated methods for sampling and analysis shall be used as appropriate for a verification protocol. If the testing results in residue levels that are unacceptable, the equipment shall be recleaned and retested until acceptable residues are achieved. Such a "clean until clean" approach is acceptable for a verification mode.

15. DIRTY AND CLEAN HOLD TIMES

The dirty hold time (DHT) is defined as the time from the end of manufacture until the beginning of the validated cleaning process. The clean hold time (CHT) is defined as the time from the end of the validated cleaning process until the beginning of the use of that equipment for manufacture of products.

15.1 Dirty Hold Time

For cleaning processes, a defined DHT shall be specified in the WI. The worst-case condition for the DHT shall constitute a challenge to the cleaning process in the cleaning validation protocol.

15.2 Clean Hold Time

For cleaning processes, a defined CHT shall be specified in the WI.

For cleaning processes utilizing volatile organic solvents (such as acetone) or volatile organic solvent/water mixtures (such as isopropanol in water) as the final cleaning rinse, and in which the cleaned equipment is protected from external contamination, bioburden proliferation in storage is not a significant risk. In such cases, a default CHT of 72 hours shall be utilized without the need to collect data in a formal CHT protocol. If the default CHT is exceeded, then the equipment shall be cleaned with a final rinsing step in the previous cleaning procedure, and production should begin with 72 hours.

For cleaning processes utilizing only water as the final cleaning rinse, and in which the cleaned equipment is protected from external contamination, bioburden proliferation in storage is not a significant risk for a short time. In such cases, a default CHT of 24 hours shall be utilized without the need to collect data in a formal CHT protocol. If the default CHT is exceeded, then the equipment shall be rinsed with 70% isopropanol or sanitized with hot (≥ 180°F) water for a minimum of 20 minutes surface contact at ≥ 180°F, followed by a Purified Water, USP rinse of equipment, and production should begin with 24 hours.

If a time longer than the default CHT is desired, a protocol shall be performed to determine that the cleaned equipment maintains a clean state for the storage time and conditions. The acceptance criteria for such a protocol shall include visual cleanness and a lack of bioburden proliferation during the CHT. Lack of bioburden proliferation shall mean that the equipment meets the least stringent criteria of the cleaning validation bioburden acceptance criterion (Section 9.4) and a one-log increase from the baseline bioburden at the beginning of the storage time. If the validated CHT limit is exceeded, then the equipment shall be cleaned with a final rinsing step of the previous cleaning procedure, and production should begin within 72 hours for a solvent or solvent/water rinse, or 24 hours for a water rinse.

16. EQUIPMENT DOCUMENTATION

In order to appropriately calculate residue limits and to appropriately determine surfaces requiring recovery studies, Aphena shall maintain a summary database of equipment to include the following:

- Equipment description
- Equipment serial number
- Total product contact surface area of equipment
- Materials of construction of product contact surfaces

- Product contact surface areas of individual materials of construction

17. MAINTENANCE OF VALIDATED STATE

17.1 Change Control

Any changes in equipment, batch size, product mix, cleaning agent, cleaning agent concentration, cleaning agent composition, method of application, residue limits, product campaign duration, addition of new product to equipment, and/or product formulation shall be evaluated for impact on any validated cleaning process. Such evaluation shall be documented as part of Aphena's change control program. Such an evaluation will determine what studies, data or protocols (if any) are necessary to maintain the validated state.

17.2 Revalidation

Upon any *significant* change as determined in the change control evaluation, validation shall be performed on the revised situation. While it is technically not re-validating an old process, such a process has been conventionally called "revalidation".

17.3 Routine Monitoring

Routine monitoring may include such activities as visual observation after cleaning, records of cleaning process parameters such as time, temperature, and pressure in automated cleaning processes, and any chemical or microbiological rinse water testing for cleaning processes. Such routine monitoring to be performed on a validated cleaning process shall be described in the cleaning validation protocol, and then included in the cleaning procedure.

After validation protocols are complete and during routine monitoring of manual cleaning processes by visual observation of equipment surfaces, if those cleaned surfaces are observed to be not visually clean, and if the pattern of failure is clearly an indication of operator error, then upon agreement of the production supervisor and quality manager the entire equipment item shall be cleaned again by the same cleaning process either by the same operator after retraining or by another trained operator, Such recleaning shall not constitute a deviation under Aphena procedures, but the recleaning event shall be captured in the batch record and such recleaning event shall be trended to identify possible needs for improvement in the cleaning procedure and/or in operator training. An example of a "visually clean" observation falling under this situation is a pattern of visible residues on a cleaned surface that is consistent with the direction of wiping in a manual process.

18. DEALING WITH NON-DRUG PRODUCTS

If both drug and non-drug products are processed on the same equipment, then for validation of the drug products, acceptance limits shall be evaluated based on possible cross-contamination of the non-drug products as well as the drug products.

For non-drug products made on the same equipment as drug products, cleaning processes may be validated or may be verified each time. If validated, they may be grouped with one or more drug products as long as a drug product is the worst case on which the validation protocol is performed. The only acceptance criteria required for non-drug products, provided they are validated or verified separately from drug products, are limits for cleaning agent/detergent and for bioburden, as well as the requirement that the equipment be visually clean.

19. REFERENCES

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20. GLOSSARY OF TERMS AND ACRONYMS

See also the glossary of terms and acronyms in Aphena Validation Master Plan XXXXX.

Acronym/Term	Definition
Cleaning Validation Acceptance Limit	The amount or concentration of residue above which possible contamination or co-mingling with the next manufactured batch of product would be considered unacceptable. An acceptance limit may be established for a swab sample and/or a rinse sample.
CIP	Acronym for Clean-In-Place
COP	Acronym for Clean-Out-of-Place
Cleaning	The removal of product and/or cleaning process residues from a surface to effectively reduce to an acceptable risk the potential of cross contamination of the next product being processed. Cleaning may or may not employ cleaning agents (such as detergents and/or disinfectants).
Cleaning Validation	The process of establishing that a cleaning procedure will consistently and effectively remove product and/or cleaning process residues from a particular piece of product-contact equipment to pre-determined levels.
Cleaning Verification	Approved, documented evidence that the employed cleaning method and systems will remove residue from a surface. Cleaning verification involves sampling and analysis for a specific cleaning event.
Clean Hold Time	The maximum time from the completion of cleaning until the beginning of the equipment's next use.
Dirty Hold Time	The maximum time from the end of product manufacture until the beginning of the cleaning process.
Equipment Grouping	A cleaning validation strategy in which the same or equivalent product contact parts that are used to manufacture the same products are considered as a group, and validation of cleaning on one equipment item or line also applies to other equivalent equipment items or lines for the same products.
Manufacture	As used in this CVP, manufacture includes processes involving blending of a formulation.
Packaging	As used in this CVP, packaging involves only the primary packaging of a formulation.
Product Grouping	A cleaning validation strategy in which products manufactured on the same or equivalent equipment and cleaned by the same process are considered as a group, and validation is performed on the worst-case (or most difficult-to-clean) product. In such a strategy, the validation of cleaning on the worst-case product also applies to all other products in the group.

Acronym/Term	Definition
Sampling Recovery	Laboratory method of determining the percentage recovery of a target residue from a specified surface using a specified sampling procedure and a specified analytical method.
TOC	Acronym for the analytical procedure Total Organic Carbon.
Visibly Clean	Containing no observable product, processing aid or cleaning agent residues that can be seen by the unaided eye in ordinary lighting.
Product-contact Surfaces	Equipment surfaces that directly or indirectly contact the manufactured product such that residues may be transferred from the surface to the manufactured product.

APPENDIX A: Calculating Acceptance Limits for Actives for Oral Dosage Forms

The residue limit for a drug active shall be established based on the calculations below. These calculations are based on the standard 0.001 dose carryover of the active of the cleaned product into the next manufactured drug product. Note that the limit for swab sampling is a concentration in the extracted swab sample, and the limit for a rinse solution is a concentration limit in the rinse solution.

For swab sampling:

$$L_S = \frac{\text{(Min. dose) X 1000 X (Batch size) X (Swab Area)}}{\text{(SF) X (Max. dose) X (Surface Area) X (Extraction Volume)}}$$

Where

L_S = limit per extracted swab sample, in micrograms/gram (µg/g)
Min. dose = the minimum daily dose of the *drug active* in the cleaned product, in milligrams (mg)
Batch size = batch size of the subsequently manufactured product, in grams
Swab Area = area swabbed, in inch^2
SF = safety factor (usually 1,000)
Max. dose = the maximum daily dose of the subsequently manufactured *drug product*, in grams
Surface area = total combined surface area of the product contact parts, in inch^2
Extraction Volume = the volume of solvent the swab is extracted in to, in grams

Note 1: In these calculations, 1000 in the numerator is to convert from mg to µg.

Note 2: If the term $\frac{\text{(Min. dose) X 1000}}{\text{(SF) X (Max. dose)}}$ is greater than 10 ppm (10 µg/g), then the limit per swab shall be calculated as:

$$L_S = \frac{\text{10 µg/g X (Batch size) X (Swab Area)}}{\text{(Surface Area) X (Extraction Volume)}}$$

Note 3: To convert these limits from µg/g of active to µg/g of TOC, multiply the limit by the percent of TOC (expressed as a decimal) in the active.

Note 4: If either or both products are dosed on a frequency other than daily, the doses for the two products must be normalized to compare them on the same period (both daily, both weekly, etc.).

Note 5: For packaging operations in which products are filled and refilled into a hopper for packaging, the "Batch size" should be considered one hopper full of product.

For rinse sampling:

$$L_R = \frac{\text{(Min. dose) X 1000 X (Batch size) X (Area sampled)}}{\text{(SF) X (Max. dose) X (Surface area) X (Rinse volume)}}$$

Where

L_R = limit for rinse solution in micrograms/milliliter (µg/mL)
Min. dose = the minimum daily dose of the *drug active* in the cleaned product, in milligrams (mg)
Batch size = batch size of the subsequently manufactured product, in grams (g)
Area sampled = product contact part surface area rinsed, in inch^2

SF = safety factor (usually 1,000)
Max. dose = the maximum daily dose of the subsequently manufactured *drug product*, in grams
Surface area = total combined surface area of the product contact parts, in $inch^2$
Rinse volume = the volume in mL of the rinse from which a sample (for testing) is taken

Note 1: In these calculations, 1000 in the numerator is to convert from mg to µg.

Note 2: If the term $\frac{\text{(Min. dose) X 1000}}{\text{(SF) X (Max. dose)}}$ is greater than 10 ppm (10 µg/g), then the limit per rinse sample shall be calculated as:

$$L_R = \frac{\text{10 µg/g X (Batch size) X (Area sampled)}}{\text{(Surface Area) X (Rinse volume)}}$$

Note 3: To convert these limits from µg/mL of active to µg/mL of TOC, multiply the limit by the percent of TOC (expressed as a decimal) in the active.

Note 4: If either or both products are dosed on a frequency other than daily, the doses for the two products must be normalized to compare them on the same period (both daily, both weekly, etc.).

Note 5: For grab samples at the end of the final process rinse (as in CIP cleaning), the calculations above are used with the “Area sampled” being the total surface area of the equipment and “Rinse volume” being an estimate of the volume of a separate sampling rinse if such a separate sampling rinse were used. Values to use for such estimate include the volume for riboflavin coverage studies to contact all surfaces, the volume of the final rinse for pulsed or burst rinses, and 5% of the equipment volume.

Note 6: For packaging operations in which products are filled and refilled into a hopper for packaging, the “Batch size” should be considered one hopper full of product.

APPENDIX B: Calculating Acceptance Limits for Actives for Topical Dosage Forms

The residue limit for a drug active shall be established based on the calculations below. These calculations are based on the standard 0.001 dose carryover of the active of the cleaned product into the next manufactured drug product. Because the topical dosage forms manufactured at Aphena are not designed to be systemically available (such as by transdermal penetration), the therapeutic effect of the drug active is limited to the skin area the products are applied to. If both products can be applied "as needed" on an indefinite frequency, the concentration limit of the active of the cleaned product in the next topical drug product can be simplified to 0.001 of the concentration of the active in the cleaned product. Note that the limit for swab sampling is a concentration in the extracted swab sample, and the limit for a rinse solution is a concentration limit in the rinse solution.

For swab sampling:

$$L_S = \frac{(\text{Conc. active}) \times 10^4 \times (\text{Batch size}) \times (\text{Swab Area})}{(\text{SF}) \times (\text{Surface Area}) \times (\text{Extraction Volume})}$$

Where

L_S = limit per extracted swab sample, in micrograms/gram (µg/g)
Conc. Active = percent concentration of *active* in the cleaned product (2% is 2, not 0.02)
Batch size = batch size of the subsequently manufactured product, in grams
Swab Area = area swabbed, in $inch^2$
SF = safety factor (usually 1,000)
Surface area = total combined surface area of the product contact parts, in $inch^2$
Extraction Volume = the volume of solvent the swab is extracted into, in grams

Note 1: In these calculations, 10^4 in the numerator is to convert from a percentage to µg/g.

Note 2: If the term $\frac{(\text{Conc. Active}) \times 10^4}{(\text{SF})}$ is greater than 10 ppm (10 µg/g),
then the limit per swab shall be calculated as:

$$L_S = \frac{10\ \mu g/g \times (\text{Batch size}) \times (\text{Swab Area})}{(\text{Surface Area}) \times (\text{Extraction Volume})}$$

Note 3: To convert these limits from µg/g of active to µg/g of TOC, multiply the limit by the percent of TOC (expressed as a decimal) in the active.

Note 4: For packaging operations in which products are filled and refilled into a hopper for packaging, the "Batch size" should be considered one hopper full of product.

For rinse sampling:

$$L_R = \frac{(\text{Conc. Active}) \times 10^4 \times (\text{Batch size}) \times (\text{Area sampled})}{(\text{SF}) \times (\text{Surface area}) \times (\text{Rinse volume})}$$

Where

L_R = limit for rinse solution in micrograms/milliliter (µg/mL)
Conc. Active = percent concentration of *active* in the cleaned product (2% is 2, not 0.02)
Batch size = batch size of the subsequently manufactured product, in grams (g)

Area sampled = product contact part surface area rinsed, in $inch^2$
SF = safety factor (usually 1,000)
Surface area = total combined surface area of the product contact parts, in $inch^2$
Rinse volume = the volume in mL of the rinse from which a sample (for testing) is taken

Note 1: In these calculations, 10^4 in the numerator is to convert from a percentage to µg/g.

Note 2: If the term $\frac{(\text{Conc. Active}) \times 10^4}{(\text{SF})}$ is greater than 10 ppm (10 µg/g),
then the limit per rinse sample shall be calculated as:

$$L_R = \frac{10\ \mu g/g \times (\text{Batch size}) \times (\text{Area sampled})}{(\text{Surface Area}) \times (\text{Rinse volume})}$$

Note 3: To convert these limits from µg/mL of active to µg/mL of TOC, multiply the limit by the percent of TOC (expressed as a decimal) in the active.

Note 4: For grab samples at the end of the final process rinse (as in CIP cleaning), the calculations above are used with the “Area sampled” being the total surface area of the equipment and “Rinse volume” being an estimate of the volume of a separate sampling rinse if such a separate sampling rinse were used. Values to use for such estimate include the volume for riboflavin coverage studies to contact all surfaces, the volume of the final rinse for pulsed or burst rinses, and 5% of the equipment volume.

Note 5: For packaging operations in which products are filled and refilled into a hopper for packaging, the “Batch size” should be considered one hopper full of product.

APPENDIX C: Calculating Acceptance Limits for Cleaning Agents/Detergents

The residue limit for the detergent shall be established based on the calculations below. In these calculations, the detergent limit is expressed based on the detergent product concentrate as purchased.

For swab sampling:

$$L_S = \frac{(0.00001) \times (LD50) \times (Body\ Wt.) \times 10^3 \times (Batch\ size) \times (Swab\ Area)}{(Max.\ dose) \times (Surface\ Area) \times (Extraction\ Volume)}$$

Where

L_S = limit per swab, in micrograms per swab
LD50 = animal acute 50% lethal dose, by the same route of administration (e.g., oral or intravenous) as the *subsequent drug product*, in milligrams per kilograms of body weight
Body Wt. = average body weight of patients to whom the drug is administered, in kg
Batch size = batch size of the subsequently manufactured product, in grams
Swab Area = area swabbed, in inch^2
Max. dose = maximum dose of the subsequently manufactured *drug product*, in grams
Surface area = total surface area of the equipment train, in inch^2
Extraction Volume = the volume of solvent the swab is extracted into, in grams

Note 1: If the term $\frac{(0.00001) \times (LD50) \times (Body\ Wt.) \times 10^3}{(Max.\ dose)}$ is greater than 10 ppm (10 µg/g) based on detergent solids, then the limit per swab shall be calculated as:

$$L_S = \frac{10\ \mu g/g \times (Batch\ size) \times (Swab\ Area) \times (RF)}{(Surface\ Area) \times (Extraction\ Volume)}$$

Note 2: For packaging operations in which products are filled and refilled into a hopper for packaging, the "Batch size" should be considered one hopper full of product.

For rinse sampling:

$$L_R = \frac{(0.00001) \times (LD50) \times (Body\ Wt.) \times 10^3 \times (Batch\ size) \times (Area\ sampled)}{(Max.\ dose) \times (Surface\ Area) \times (Rinse\ volume)}$$

Where

L_R = limit in the rinse sample, in micrograms per milliliter (µg/mL)
LD50 = animal acute 50% lethal dose, by the same route of administration (e.g., oral or intravenous) as the subsequent drug product, in milligrams per kilograms of body weight
Body Wt. = average body weight of patients to whom the drug is administered, in kg
Batch size = batch size of the subsequently manufactured product, in grams
Area sampled = equipment surface area rinsed, in inch^2
Max. dose = maximum dose of the subsequently manufactured *drug product*, in grams
Surface area = total surface area of the equipment train, in inch^2
Rinse volume = volume of rinse solution, in milliliters

Note 1: If the term $\frac{(0.00001) \times (LD50) \times (Body\ Wt.) \times 10^3}{(Max.\ dose)}$ is greater than 10 ppm (10 µg/g) based on

detergent solids, then the limit in the rinse sample shall be calculated as:

$$L_R = \frac{10\ \mu g/g \times (\text{Batch size}) \times (\text{Area Sampled}) \times 100}{(\%\ \text{Detergent solids}) \times (\text{Surface Area}) \times (\text{Rinse volume})}$$

Note 2: In both of these calculations, 0.00001 (10^{-5}) represents the combined conversion and safety factor to convert an LD50 to an ADI (Acceptable Daily Intake), and 10^3 represents the conversion factor from milligrams to micrograms.

Note 3: If the detergent is measured by TOC, conversion of the limit of the cleaning agent to an equivalent TOC value can be made by multiplying the limit calculated above by the percent of carbon in the cleaning agent expressed as a decimal.

Note 4: For grab samples at the end of the final process rinse (as in CIP cleaning), the calculations above are used with the “Area sampled” being the total surface area of the equipment and “Rinse volume” being an estimate of the volume of a separate sampling rinse if such a separate sampling rinse were used. Values to use for such estimate include the volume for riboflavin coverage studies to contact all surfaces, the volume of the final rinse for pulsed or burst rinses, and 5% of the equipment volume.

Note 5: For packaging operations in which products are filled and refilled into a hopper for packaging, the “Batch size” should be considered one hopper full of product.

Appendix D: Decision Tree for Determining Need for Cleaning Validation