Microbial Contamination and Control Conference

Cleaning Validation for Commercial Manufacturing Lifecycle

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WHAT IS CLEANING VALIDATION?

- "Documented evidence that an approved cleaning procedure will reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum carry over level." Euradex Volume 4, Annex 15
- Numerous Regulations and Guidance – all align on the principle that products are safe, efficacious and free from adulteration by other components and contaminants.
- There are differences in the various regulations (i.e. application of HBELs, risk management)

FDA Warning Letter to K.C. Pharmaceuticals Inc. 8/3/2023

- **3. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).**
- Cleaning validation studies for aseptic processing line **(b)(4)**, used to manufacture multiple formulations of ophthalmic drug products, has not been completed. For example, the **(b)(4)** compounding tank and product transfer line **(b)(4)**, used to formulate bulk ophthalmic drugs for filling on line **(b)(4)**, did not have recovery studies or limits of detection. Additionally, when identifying the **(b)(4)** conditions under which to conduct the cleaning validation, you relied only on the viscosity of your multiple ophthalmic drug products to make the determination, omitting other factors that can make certain formulations harder to clean. While you chose the product Eye Drops Systane-Ultra Like (EDSU) as **(b)(4)**, you lacked documented scientific evidence to support use of **(b)(4)** viscosity as adequate basis for validating the hardest to clean product surface.
- In response to this letter, provide:
- Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as **(b)(4)** in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all **(b)(4)**:
- o drugs with higher toxicities
  o drugs with higher drug potencies
  o drugs of lower solubility in their cleaning solvents
  o drugs with characteristics that make them difficult to clean
  o swabbing locations for areas that are most difficult to clean
  o maximum hold times before cleaning
- In addition, describe the steps that must be taken in your change management system before introduction of new manufacturing equipment or a new product.
- A summary of updated standard operating procedures (SOPs) that ensure an appropriate program is in place for verification and validation of cleaning procedures for products, processes, and equipment.

WHY DO WE DO PERFORM CLEANING VALIDATION?

- Patient Safety
- Prevent contamination of products
- Compliance with regulatory requirements
- Good Business Practice

Why is the process so rigorous?

- How do we define clean?
- Is “visually clean” enough?
- How do we know the cleaning procedures are appropriate? Manual vs. automated?
- Are the cleaning agents effective? Are they safe and fully removed from the process?
- What is the risk to the patient of carry over to the next product? How are limits set and methods validated?
- Are microbial contaminants removed?
- Is the storage of equipment harboring growth of microorganisms?

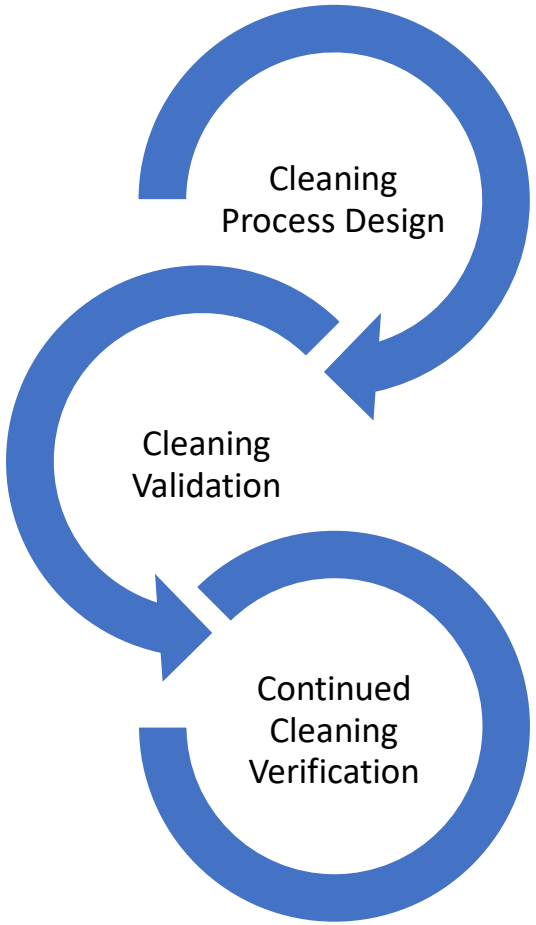
How to set up a successful cleaning validation program?

- Need a cross functional team that includes:

-Analytical chemistry	-Toxicology
-Medical affairs	-Manufacturing/Process engineering
-Facilities engineering	-Validation engineering
-Quality Assurance	-Microbiology
-Health and Safety	-Manufacturing/operations personnel

- A thorough understanding of the cleaning process with well written procedures and training.
- Cleaning Validation Master Plan that addresses the comprehensive strategy based on: products, equipment, cleaning processes.
- Effective change management and continued cleaning verification.

Cleaning Validation Lifecycle



- Stage 1 Cleaning Process – Design a cleaning process to avoid and reduce risks of contamination and cross contamination
- Stage 2 Cleaning Validation – Qualification phase with trained operators to gather evidence to support cleaning process design.
- Stage 3 Continued Cleaning Process Verification – On going monitoring of the cleaning process that includes: change management, routine sampling, periodic monitoring, and revalidation

Stage 1 – Cleaning Process Design

Risk Assessment

- Residue Characterization
- Cleaning Agents
- Equipment Design
- Cleaning Process (TACT)
- Determine Critical Process Parameters and Criticality
- Define and Justify Residue Limits
- Select Analytical Methods
- Select Microbial Methods
- Define Sampling Methods
- Perform Residue Recovery Studies
- Define Acceptance Criteria
- Conduct Small Scale Studies

Residue Characterization

Contaminants to be removed from the process equipment

- From previous products
  - Active Pharmaceutical Ingredients
  - Excipients
  - Process aids/materials
- From cleaning agents/disinfectants
- From environment (airborne)
- Analytical Method specific vs. non-specific

- Assess process impact
  - Fresh, immediate after use
  - Dried during process
  - Dried during dirty hold time
  - Baked during process
  - Compacted
  - Solubility
  - Cleanability
  - Degradation or deactivation of residues

Cleaning Agents, Cleaning Cycles

Selection of cleaning agent should be scientifically justified and based on:

- Ability to remove target residues, general rules

Acidic	Alkaline	Neutral	Concentration
Minerals	Proteins	pH sensitive materials	Based on Quantity and
Inorganic Soils	Organic Soils		Condition of Soil
Alkaline Soils	Acidic Soils		

  - Watch Outs: No Foaming, Material Compatibility, Neutralization Issues
- Compatible with equipment materials of construction
- Safety of cleaning agent (toxicity)
- Ease of removal and ability to detect absence of

Equipment Design

- Equipment Design and Construction
  - Direct product contact surfaces
  - Indirect product contact surfaces
  - Non-product contact surfaces (utensils)
- Cleanability of
  - Critical Equipment Parts
  - Hard to clean equipment locations
  - Ability to drain, sloping, drying
  - Surface condition (scratches, pitting)
  - Coverage studies (riboflavin)
- Equipment use
  - Dedicated vs. non-dedicated
  - Campaign length (batches or times)
  - Dirty Hold Time (DHT)
  - Clean Hold Time, parts storage
  - Equipment Maintenance (passivation)
  - Clean In Place (CIP skid)
  - Clean Out of Place

Cleaning Process TACT

- Define and establish TACT parameters

Temperature

Action/**A**gitation

Concentration/**C**hemistry/**C**leaning agent

Time

Applies for ALL pre-wash, wash, rinsing and drying steps

Applies to CIP and COP

Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs)

- Identify cleaning process parameters and justification of which ones are critical for process effectiveness. Must be reproducible for both manual and automated systems.

Critical Process Parameters Examples	Critical Quality Attributes Examples
Process Temperature	Visual Inspection
Process Pressure / Flow	Chemical Residue Limits
Process Time	Microbiological Residue Limits
Cleaning Agent Concentration	Drainability / Drying
Clean Hold Time (CHT)	Conductivity / Resistivity
Dirty Hold Time (DHT)	Cleaning Agent Residue Limits

Residue Limits - Analytical

- Limits shall be practical, logical, achievable and verifiable
- Rationale needs to be based on components involved and therapeutic dose
- Health Based Exposure Limits (HBELs) relies on toxicological and/pharmacological data. Typically, PDEs (permitted daily exposure)
- HBELs assure the Maximum Allowable Carry Over (MACO) – or the maximum allowable of carry over residue of a previous product, cleaning agent or ANY residue, into the next product being manufactured on the same equipment.

MACO Calculation (simplified example)

$$MACO\ [\mu g] = \frac{PDE\ \left[\frac{mcg}{day}\right] \times Next\ Min\ Batch\ Size\ [L]}{Max\ Daily\ Dose\ \left[\frac{mL}{day}\right]}$$

- The maximum total amount of carryover to the next product batch
- Determine the maximum amount per surface area (in µg/cm2)
- Determine the maximum amount per swab (in µg), or the maximum concentration in a desorbed swab sample or a rinse sample (in µg/g or µg/mL)

Equipment Grouping Train 1 (Tanks X,Y,Z Transfer Line, Filler)

Product Name			Product A	Product B	Product C
	Batch Size (L)		250	200	250
	PDE (mcg/day)	MDD (mg/day)	84.0	19.6	160.0
Product A	375			19.1	2.3
Product B	19365		230.3		121.0
Product C	500		5.9	25.5	

Product Worst Case Selection

- Worst case product selection "most difficult to clean" is based on:
  - Difficult to clean – historical knowledge or bench studies
  - Solubility (individual components, product)
  - Formulation (water based, emulsion, processing challenges)

- Residue Limit
  - Worst case product and lowest MACO of shared surface area

Residue Limits - Microbiological

- Limits should be established based on risk assessment considering the following:
  - Finished product specification
  - Manufacturing room environment and personnel exposure
  - Cleaning agent disinfectant efficacy
  - Equipment Materials of Construction
  - Rinse water quality (refer to USP <1119>)
  - Equipment Drying Process and Challenges
  - Clean and Dirty Part Storage
- Bioburden limits are necessary to establish a clean hold time
- Determine Routine Monitoring Strategy

Visible Residue Limits (VRL) – when applicable

- VRL is a quantified visual level of residue that trained operators have demonstrated successful visual detection
- NOT VISUALLY CLEAN
- Can be a stand-alone study or can be used in conjunction with swab and rinse methods.
- Spiking studies with known concentration, visually examined in control setting (lighting, angle, distance, viewer) – need to demonstrate reproducibility

Determine Analytical Methods

Analytical methods need to assess:

- method selectivity (for product specific methods),
- limit of Detection (LOD) / Limit of Quantitation (LOQ)
- method validation status

- Specific methods are preferred, however if not feasible to test for specific residues, other representative parameters may be selected.
- For example, TOC (Total Organic Carbon) may be used – rationale needed.

Define Sampling Methods

- Visual inspection first
- Rinse samples (analytical, bioburden, BET)
  - Covers large surfaces as provides an overall picture
  - Rinse curves can help establish effective rinse cycle times
- Swab samples (analytical and bioburden)
  - Worst case locations (hardest to clean) – team assess locations - need rationale
  - Sample locations materials of construction
  - Sampling medium/solvent
  - Technique and Training

Residue Recovery Studies

- Rinse and Swab Recovery Studies
  - Representative materials of construction – coupon studies, representative surfaces
  - Apply recovery factor in limit calculation
  - Spike a coupon with a known amount (typically active)
  - Perform 3 replicates

  Acceptable recovery rates- compare to expected 100% recovery rate

  >80% = good

  >50% = acceptable

  <50% = further investigate

Define Acceptance Criteria

- Acceptance criteria needs to be defined at this stage.
- In cleaning validation stage 2, the acceptance criteria needs to be documented with scientific rationale.
- Potential residue limits include: active ingredient, product residues, cleaning agent, bio load, degradation products
- Typically Include: visual inspection, swab, rinse, micro, endotoxin, reproducibility (successful consecutive runs)

Stage 2 – Cleaning Process Qualification/Validation

Risk Control

- Complete Equipment Qualification
- Validate Analytical and Microbiological Methods
- Define Validation Strategy, Number of Runs
- Define Sampling Plan
- Write Cleaning SOPs
- Write Cleaning Validation Protocol
- Train Personnel
- Execute Cleaning Validation Protocol
- Write Cleaning Validation Report

Equipment Qualification

Equipment qualification activities precede cleaning validation activities.

- Verify equipment operates as designed.

Recommended tests for equipment qualification include:

- Visualization agents (e.g. riboflavin tests)
- CIP cycle qualifications

Any utilities and corresponding distribution systems (water, clean steam, compressed gases) supporting cleaning validation shall be qualified.

Validate Analytical and Micro Methods

Analytical method readiness includes identification of those analytical methods that need to be validated in accordance with ICH Q2 and transferred to the appropriate testing laboratory and should include:

- Accuracy
- Precision
- Range
- Linearity and selectivity
- Limit of Detection and Limit of Quantitation

Sampling methods via rinse or swab should also be validated.

- Bioburden and endotoxin testing must be validated.

Validation Strategy

Typically includes execution of the cleaning process on soiled equipment to demonstrate the effectiveness and reproducibility of the cleaning process.

The protocol must identify and justify the number of cleaning runs

- Clean hold time (CHT: the amount of time cleaned equipment can remain in a clean state),
- Dirty hold time (DHT: the amount of time soiled equipment can remain dirty before cleaning) and the amount of time in the drying process.
- The number of runs performed within the validation shall be based on knowledge (process understanding) as well as the overall risk to product, including process monitoring. The rationale to justify the number of runs must be documented. The rationale can be based but not limited, on the following: development studies, the equipment under validation, risk controls in place, and relative product risk.
- Campaign production of successive batches of the product is used, equipment shall be cleaned at appropriate intervals to prevent build up and carry-over of contaminants; intervals depend on susceptibility to microbial growth and/or product degradation.

Sampling Plan

Sample plan shall describe:

- Sample locations
- Number of samples
- Swab sampling
- Rinse Sampling
- Visual Inspection

- Sampling methods shall be appropriate for the analyte being measured. Analytical method validation and recovery studies shall be established for all worst case product residues, materials of construction and chemical cleaning agents.
- Validation activities shall be carried out using the worst case product (component) as this is used as an indicator of cleaning method robustness

Visual Inspection Criteria

Visually Clean (VC) equipment shall be visually examined for visual cleanliness following the cleaning validation cycle.

Visually acceptable based on the evidence of:

- absence of foreign material (product, degradants, soiling agents, etc.), for example no visual discoloration, clumps, particulates, coating, or film.
- verification of draining and/or drying of equipment.
- The human eye cannot typically detect residues under 5mg/cm^2

Visually clean (VC) provides a high level of confidence that equipment is sufficiently clean, however additional sampling (direct surface, rinse) are also required to support cleaning validation.

- Visible Residue Limit (VRL) Study can be a stand-alone cleaning validation process (when no additional analytical or microbiological testing occurs) where the lowest residue amount that is visible to all qualified observers under defined viewing conditions is the visual detection limit for the product. The VRL must be quantified and shall have acceptable hazard levels based on the HBELs.
- Any residue observed is typically unacceptable.

Write Cleaning SOPs

SOPs describe the steps and specific instructions required to execute a cleaning process.

- Automated systems shall have system configurations with appropriate parameters defining the sequence of steps to be executed for cleaning
- Critical process parameters (CPPs) shall be clearly documented
- It is required to identify the types of equipment (e.g. non-dedicated or dedicated), cleaning agents, and cleaning processes (e.g. manual or automated), critical control parameters.
- A draft or already implemented procedure may be used in validation

Write Cleaning Validation Protocol

Cleaning validation protocol needs to document the strategy and be approved prior to execution. Validation protocol content should include:

- Cleaning procedure to be validated (CPPs)
- Products (grouping) covered
- Description of equipment, surface area (grouping covered)
- Residues to be removed
- Number of runs, and rationale
- Analytical and micro methods (validated, LOD/LOQ)
- Sampling method
- Acceptance Criteria, reference to calculations
- Maximum DHT – effects of drying of soil, microbial proliferation, difficult removal
- Maximum CHT - microbial proliferation and external contamination

Training

Operators, laboratory technicians, samplers, and inspectors must have the necessary education and experience and are trained on SOPs related to the cleaning process and on the cleaning validation protocol content and objectives.

- Personnel may receive on-the-job training to be able to execute procedures
- Training shall include how to document observations correctly (e.g. visual inspections) and detect unexpected events.

Execute Cleaning Validation Protocol

- Approved cleaning validation protocols are executed and data (e.g. parameters, observations, CIP cycle start/stops) is documented for assessment against cleaning method process, critical process parameters, and acceptance criteria.
- Record all parameters and use of any cameras, magnifiers, flash lights, mirror, boroscope for inspections.
- Any cleaning validation, or routine monitoring testing failure requires an investigation.

Write Cleaning Validation Report

- Cleaning Validation Reports should include:
  - All data generated during the study (graphs/ cycle printouts)
  - Cleaning SOP used
  - Evidence of training
  - Analysis of all runs including parameters achieved (CPPs)
  - Conclusion of the validated cleaning process and
    - DHT – dirty equipment storage time
    - CHT – clean equipment storage time
  - Assessment for routine monitoring moving forward

Stage 3 – Continued Cleaning Verification

Risk Review

Monitor Cleaning Process Performance

Conduct Periodic Reviews of Cleaning Process State of Control

Change Management

Monitor Cleaning Process Performance

- Once the process is validated, reduced sampling and testing can be implemented.
- Types of monitoring
  - Data trending
    - Trending of cleaning process parameters (TACT)
    - Trending of sampling test results
    - Trending of deviations, Out of Specification (OOS) and Alarms
  - Continuous Rinse sample nonspecific tests (in-line conductivity or TOC)
- Monitoring needs to be defined in a procedure, trends will need limits established. Data from process monitoring should be trended to detect shifts in cleaning method performance.

Periodic Reviews

A periodic review should demonstrate that the cleaning process remains in a validated state of control and consists of the following:

- Cleaning process description (scope of the review, time period)
- History of cleaning process changes
- Evaluation of cumulative impact of changes
- Summary of CPP monitoring, summary of alarms/excursions events
- Results of routine monitoring
- Review of non-routine maintenance and events
- Review of deviations and corrective actions, including visual inspection failures
- Review of recleaning cycles and justifications
- Review of changes to analytical and micro methods
- Review of equipment inspections and maintenance (rouging, scratches, leaks)

Change Management

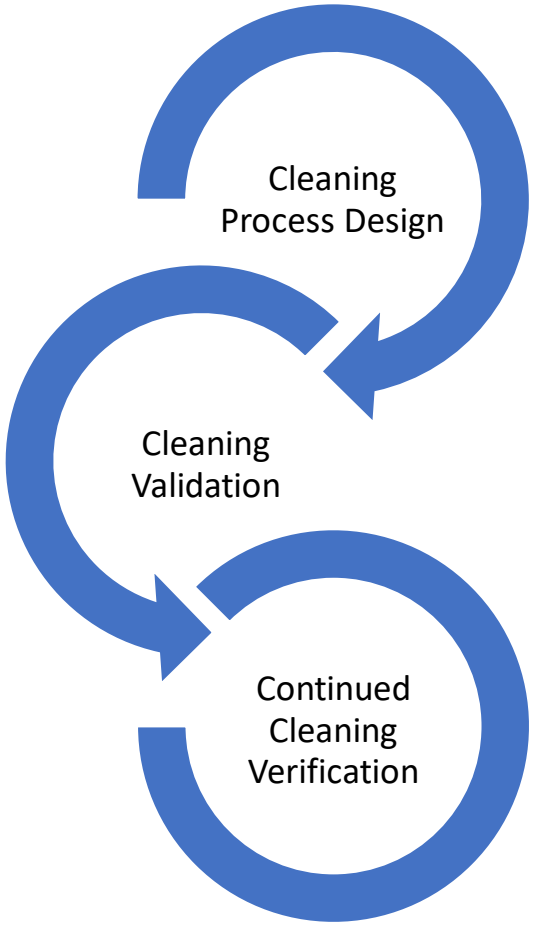
Change management is critical in assuring changes to cleaning processes are assessed for impact.

- Changes shall assess impact to CPPs and cleaning effectiveness.
- Modification of HBEL (adding new products)
- Changes should be assessed as part of periodic review.

Revalidation may be needed based on periodic review or significant changes.

Conclusion

- Cleaning Validation is a lifecycle
- Must be maintained in a state of control
- Involves multiple disciplines
- Focus of many regulators



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May 8th & 9th