Cleaning Validation & Regulatory Compliance

An Introduction & Overview

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Overview

I. REGULATORY BACKGROUND

II. TRADITIONAL VS RISK BASED APPROACHES

III. KEY REFERENCE DOCUMENTS

IV. OBJECTIVES OF THE CLEANING PROCESS

V. CLEANING VALIDATION – RISK BASED APPROACH

VI. EXAMPLES OF LIMIT CALCULATIONS

VII. CLEANING VALIDATION SUMMARY

Key Regulatory Concerns

Efficacy / Strength	**Does the validated cleaning process result in residues that do not interfere with the efficacy of the vaccine?**
Identity & Purity	**Does the validated cleaning process result in residues that interfere with the purity of the API and/or excipients in the vaccine?**
Safety	**Does the validated cleaning process result in residues that are toxic to the patient?**

FDA Risk Based Approach

From FDA presentation in June 2003

"When you know your:

- Product
- Flow-path
- Equipment and how it works
- Potential in-process and process impurities
- Validation studies and their weaknesses
- Readily available technologies at your disposal

Then, you can make intelligent, science-based decisions on your process, validations, and product, and support them during an inspection!

Know the process, equipment and human capabilities.

- System suitability
- Process capabilities
- Personnel and Training
- Clear/detailed SOPs

No matter how hard you try, you cannot inspect quality into a product"

Process Validation and Drug Quality

The basic principle of GMP is that a drug should be produced that is fit for its intended use.

- Quality, safety, and efficacy are designed or built into the product.
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing
- Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.

Manufacturers should:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product

What does this mean to a Manufacturer?

Lifetime process

Begins in discovery and ends when product is obsolete

Requires definition of attributes, criteria, decision points and analytical tools

- Critical quality attributes
- Critical product profile
- Critical impurity profile
- Process analytical technologies
- Critical sampling points and strategy
- Critical control points
- Release criteria

Focussed on patient safety, not on revenue

Useful prioritization tool
3D system risk assessment concept

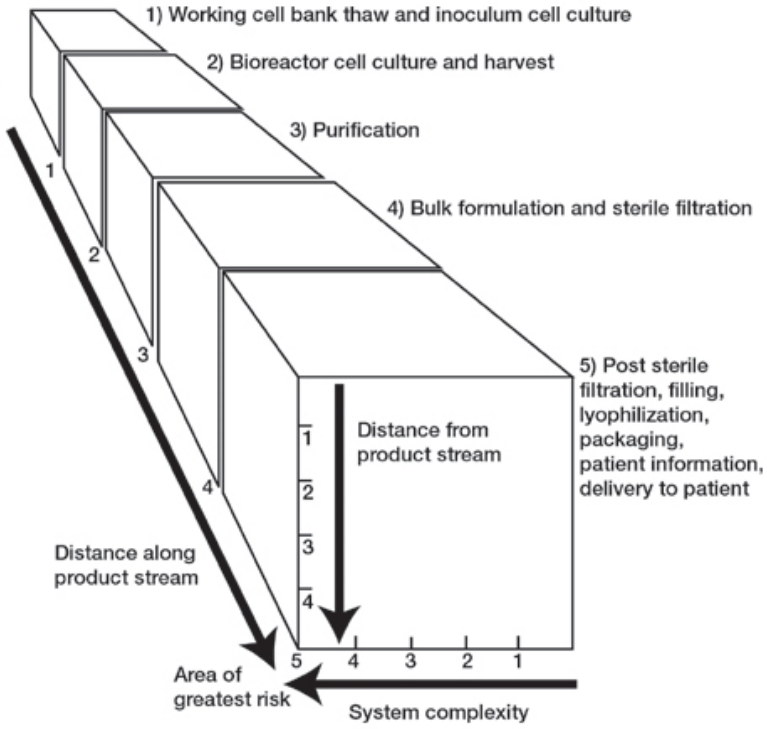
- System‘s distance from process stream
- Its location along the process stream
- The system‘s complexity

Each category has a 1-5 point scale

Similar to an RPN

Example – Sterile hold tank = 20

Distance = 5 (High),
Location = 4 (Medium / High),
Complexity = 1 (Low)



Excellent for complex systems as part of “big picture” analysis to prioritize qualification efforts

“A 3-D Risk Assessment Model”

Journal of Validation Technology

[Autumn 2008] pp70 - 76

Key Reference Document

PDA Technical Report 29 Contents
- an Ideal "Best Guide" to Cleaning Validation

1.0 Introduction

2.0 Glossary of Terms

3.0 Cleaning Process Design and Development

4.0 Qualification

5.0 Residue and Limits

6.0 Sampling

7.0 Analytical Methods

8.0 Maintenance of Validated State

9.0 Documentation

10.0 Special Considerations

11.0 Regulatory and Guidance Documents

Presentation Focus

1.0 Introduction

2.0 Glossary of Terms

3.0 Cleaning Process Design and Development

4.0 Qualification

5.0 Residue and Limits

6.0 Sampling

7.0 Analytical Methods

8.0 Maintenance of Validated State

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Cleaning Validation Regulatory Guidances

Documented evidence to establish that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, toxicology and equipment size.
(WHO TRS937)

Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing medicinal Products (*PICS PE009-10)*

”The process of providing documented evidence that the cleaning methods employed within a facility consistently controls potential carryover of product (including intermediates and impurities), cleaning agents and extraneous material into subsequent product to a level which is below predetermined levels”
(Active Pharmaceutical Ingredients Committee, Sept 1999)

Cleaning Validation – Industry Guidance

"The process of providing documented evidence that the cleaning methods employed within a facility consistently controls potential carryover of product (including intermediates and impurities), cleaning agents and extraneous material into subsequent product to a level which is below predetermined levels"

(Active Pharmaceutical Ingredients Committee, Sept 1999)

"The requirements for a Cleaning Validation Program should be defined and documented in a master plan or equivalent document."

- Points to Consider for Biotechnology Cleaning Validation, Technical Report No. 49, 2010 Parenteral Drug Association

Cleaning Validation is an extension of the VMP.

What are we trying to clean away?

Biopharm Residue Types

- Cells (animal or microbial)
- Virus
- DNA
- Proteins
- Polysaccahrides
- Degradents
- Endotoxins
- Bioburden

Other Residue Types

- Processing aids
  - Antifoams
  - Adjuvants
- Excipients
- Preservatives
- Cleaning solution residues

Cleaning Agents and Process

- **Typical Cleaning Agents**
  - Alkaline Chemical (NaOH)
  - Acidic Chemical (Phosphoric acid)
  - Oxidizer Chemical (NaOCl, >pH 7)
  - Detergent Formulation (CIP100, CIP200, Tergazyme etc)
  - Water
- **Cleaning Agent Activity**
  - Proteolyic attack, lipid solubilization
  - Hydrolysis of protein and solubilization of DNA.
  - Oxidation and proteolysis
  - Solubilization and emulsification
  - Solubilization

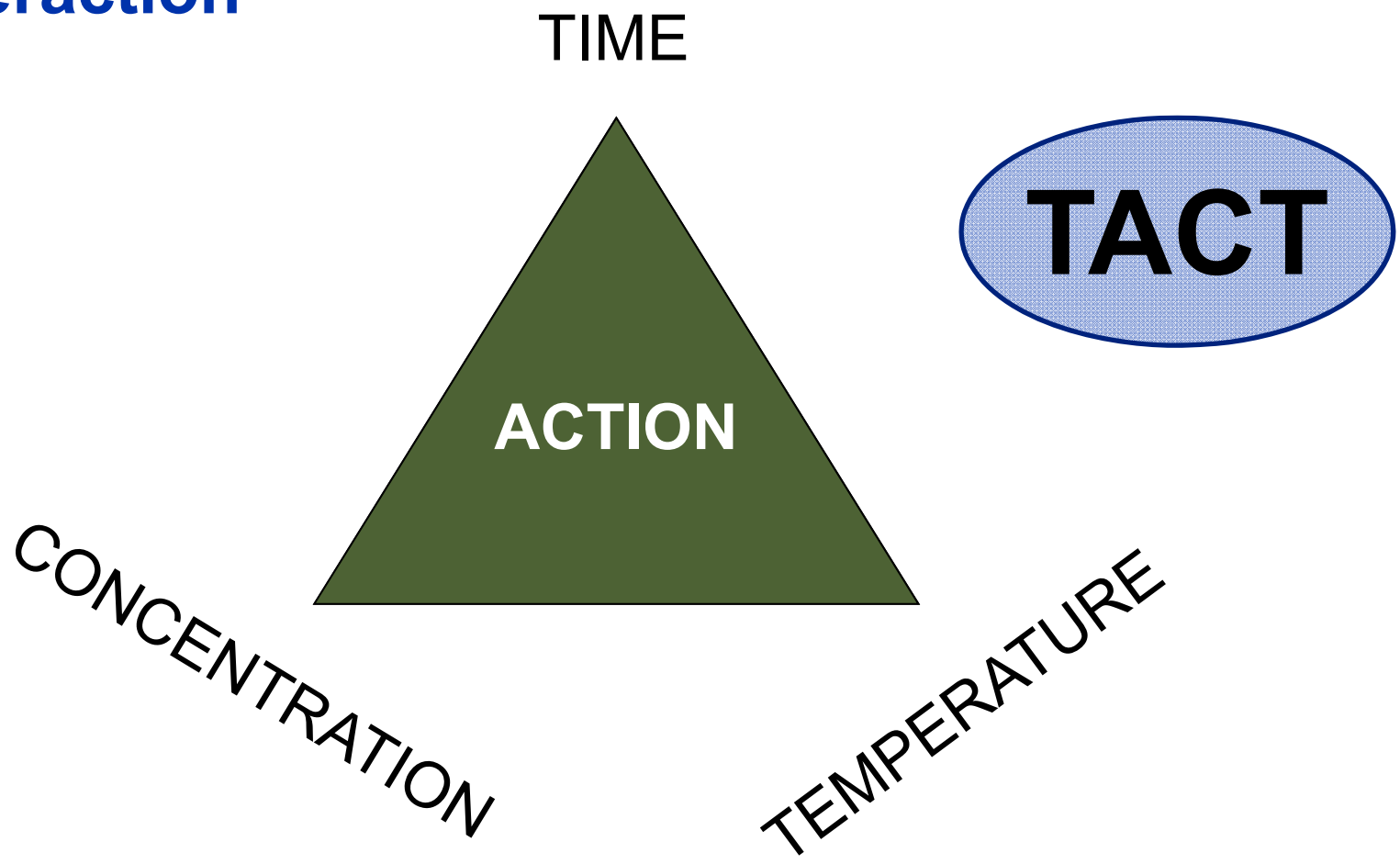
Cleaning Agents – Selection Criteria

- Suitability to remove product residues
- Compatibility with the equipment MOC
- Ease and sensitivity of assay method
- Ease of removal and verification of removal
- Low toxicity

Examples – Cleaning Agent / Application Matching

Process Fluid	Foulants	Cleaning Agents	
		Recommended	Alternative
Protein Solutions	Adsorbed protein	NaOH Tergazyme NaOCl*	Triton X-100
Bacterial whole cell broths	Adsorbed protein Antifoams Cell debris Lipids	NaOH and NaOCl	Triton X-100 or SDS followed by NaOCl
Bacterial and Yeast Lysates	Adsorbed protein LPS Cell debris	NaOH and/or NaOCl followed by H_2PO_4	Tween 80 /Triton X-100 followed by NaOCl

Effectiveness of Cleaning Agents – 4 Way Interaction



Typical Cleaning Process Design

Critical Process Parameters	Critical Quality Attributes
• Process temperature	• Visual detection or limits
• Process pressure	• Cleaning agent residues
• Process flow	• Product residues
• Process time	• Microbiological residue limits
• Cleaning agent concentration	• Drainability/drying
• Dirty hold time (soil condition)	• Conductivity/resistivity
• Clean hold conditions	

Cleaning Processes – A series of steps:

- Commence Cleaning Process before “Dirty” Hold Time Expires
- Water rinse to remove loose soils.
- Cleaning solution(s) wash (perhaps with rinses in between)
- Final Water Rinse (sampling step)
- Drain and or Dry
- Hold in a state of cleanliness until used or Clean Hold Time expires

Some Equipment Considerations

- Equipment Design
  - Sanitary Design
    - Designed to be cleaned – no crevasses deadlegs or shadowing
    - Smooth product contact surfaces - minimizes adsorptive area.
  - Design for drainability (sloped piping), Low point Drains
- Materials of Construction
  - Process Fluid Interactions - Should not be:
    - Reactive
    - Absorptive
    - Additive
  - Seals, Gaskets, hoses, valves, etc. should not add contamination.
  - Cleaning Agents compatible with MOC

Example - UF Module Cleaning Procedure

Steps	Retentate and filtrate lines	Feed Flowrate (L/min/m²)	Retentate valve position	Time or volume to flush
Buffer flush	To drain	5	Fully open	2 to 3 vol mini*
Water flush	To drain	5	Fully open	1 vol mini
	Ret.: to tank Filt.: to drain	5	Partially closed	1 to 2 vol mini
Cleaning agent 40 °C, 15 min **Retentate side**	To drain	5	Fully open	2 min
	To tank	5	Fully open	2 to 3 vol mini
Cleaning agent 40 °C, 45 min **(fresh solution)** **Permeate side**	To drain	5	Fully open	2 min
	To tank	5	Partially closed	2 to 3 vol mini
Water flush prior to NWP measurement	To Drain	5	Fully open (retentate side)	Typ. 10 to 20 L/m²**
	Ret.: to tank Filt.: to drain	5	Partially closed	Typ. 50 to 70 L/m²**

* Vol mini = system minimum working volume

** indicative volume, flush until spec is reached

Cleaning Process Variability & Controls

Sources of Variation in Cleaning Validation

- Cleaning agent quality
- Concentration of cleaning agent
- Water/solvent quality
- Time(s)
- Temperature
- TMP , Delta Pressure
- Flow
- Rinse conditions
- Dirty hold time
- Clean hold time
- Campaign length
- Manufacturing conditions
- Operator for manual cleaning

Cleaning Cycle is defined by TACT:

- Contact Time
- Action
  (Cleaning Action, Process Action
  (Flowrate, Pressure, Turbulence, etc.)
- Cleaning Reagent Concentration
- Temperature

Some Elements of Cleaning Validation Protocol

- Validation objective
- Responsibilities for performing and approving the validation study
- Description of the equipment to be used
- Interval between end of production and beginning of cleaning procedures
- Cleaning procedures to be used for each product, each manufacturing system or each piece of equipment
- Period between validation and re-validation
- Acceptance criteria and if “bracketing” is valid
- Any routine monitoring requirement, sampling procedures and clearly defined sampling locations
- Analytical methods including the limit of detection and method quantitation

Example of Steps in Cleaning Validation for Vaccines

1.Identification of Critical Control Points and Critical Process Parameters

2.Identification of sources that virus might escape during cleaning or sterilization processes.

3.Cleaning of work benches and biosafety cabinet after incubation of virus.

4.Cleaning validation of inoculum fermenter.

5.Cleaning validation of production fermenter.

6.Cleaning validation of harvesting systems

7.Cleaning validation of diafiltration systems

8.Cleaning validation of chromatography and validation of virus inactivation methods.

9.Cleaning validation of adjuvant mixing tanks.

10.Cleaning validation of incubation vessels.

11.Cleaning validation of formulation / filling tanks or vessels

12.Waste system (e.g. Kill Tank) validation of effluent from above processes

13.Environmental monitoring methods in all critical areas after disinfection of these areas.

Dedicated vs. Multi-product Equipment

Dedicated equipment should be used for;

- single products, products which are difficult to remove or have a high safety risk or that are difficult to detect at the required concentration, equipment which is difficult to clean, products with a high safety risk

Dedicated equipment is concerned about carry-over and cleaning residues

Cleaning validation for dedicated equipment / campaigns is often shorter and less complex than for multi-product equipment

Many companies **must** use equipment and support equipment for multiple products

Multi-product cleaning presents worst case

Cleaning Validation – Dedicated / Multiproduct

- If firms have one cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, we expect the written procedures to address these different scenario.,
  Validation of Cleaning Processes (7/93) GUIDE TO INSPECTIONS VALIDATION OF CLEANING PROCESSES, http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074922.htm

- **Grouping Strategy**
  - Validations of individual unit operations x multiple products – Time & Effort Intensive.
  - Grouping Strategy (Matrixing, Bracketing) is a risk based approach to CV.
  - Reduces the validation workload, while maintaining assurance that the acceptance criteria are met.

- Cleaning procedures for products and processes which are very similar do not need to be individually validated…It is considered acceptable to select a representative range of similar products and processes. .- Guidance Document, Cleaning Validation Guidelines, GUIDE-0028, January, 1 2008, Health Canada, Health Products and Food Branch Inspectorate

Cleaning Validation Design - Grouping

- Equipment Grouping Strategy Example
  - From: Risk-Based Cleaning Validation in Biopharmaceutical API Manufacturing, A. Hamid Mollah, Ph.D., Edward K. White, BioPharm International, Nov. 1, 2005,

Group ID	System Description
Media Preparation Tanks	Tanks used for media preparation
Media Hold Tanks	Tanks used for media holds
Bioreactors	Bioreactor used for API manufacturing
Bioreactor Lines	Lines used for bioreactor feed and harvest transfer
Purification Buffer Preparation Tanks	Tanks used for buffer preparations
Purification Buffer Hold Tanks	Tanks used for buffer preparations
Purification Skids	Skids used for purification process

- Product Grouping Strategy
  - Products may also be grouped in terms of “Worst Case” to clean.
- Use Risk Based tools for Justification
  - Failure Mode & Effects Analysis (FMEA), Fault Tree Analysis

Analytical Methodology

…analytical methods should be:

- **Specific**
- **Sensitive**
- **Accurate**
- **Provide results that are reliable.**
- **Procedures for analytical method and equipment maintenance, documentation practices, and calibration practices supporting process-development efforts should be documented or described**.- **Guidance for Industry Process Validation: General Principles and Practices, January. 2001, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Current Good Manufacturing Practices (CGMP) Revision 1**

- Most common Process Analytical Techniques (PAT)
  - Conductivity
  - pH
  - Total Organic Carbon
  - Others (Chlorine Assay Kit, Detergent Surfactant Kit, protein assay kit)
  - HPLC, FTIR, ELISA , total protein & Endotoxin
  - Are Specific Assays the Most Appropriate?

Sampling Methodology Comparison

- Most common Sampling Schemes
  - Rinse Samples (indirect)
  - Swabbing (direct)
  - Can be a combination of both.
- Closed system rinse sampling options
  - Sampling technology should not contaminate or cause contamination of sample
  - Examples; Novaseptum, Sta-Pure etc. for Rinse samples

Sampling Method	Pro's	Con's
Rinse	Maintains System Closure	Relies on uniform distribution of residue and covereage of reinse step
	Rinse represents all contact areas eve the "hard to reach"	Does not directly sample surface
	Analysis can be on-line or off-line	
Swab	Direct Sample of Surface	Risk of contamination higher with direct operator interface
	Sampling spot is defined	Analysis off line
		Must have very well defined procedures, training

Comparison of Sampling Procedures

Rinse and swab measure two different things so do not expect a correlation between the two

Swabs focus on small area	Rinses focus on larger area
Swab measures worst case	Rinse measures average

If both done correctly on same surfaces,

- Rinse may pass but swab may fail
- If swab passes, rinse should also pass

Establishing Acceptable Limits

Limits should be:

- Practical, achievable and verifiable
  - Example – is the WFI TOC limit an acceptable limit for a 10 m^2 system
- Logical, based on knowledge of materials
- Assuming non-uniform distribution of compounds
- Assessed on a case-by-case basis

There should be no residue from:

- Previous product, by-products and degradants
- Microbiological material or its by-products
- Cleaning process (e.g. detergents, solvents, by-products, degradants)

Limit Setting Approach

- Can be product-specific
- Allows product grouping / bracketing to choose a worst case product (based on documented scientific evidence) according to product, equipment & risk
  - very soluble products
  - products with similar potency
  - therapeutic dose
  - highly toxic products
  - difficult to detect products
- Safety factors for different dosage forms depends on physiological response / toxicity / dosage route

Cleaning Acceptance Criteria.

Acceptance Criteria - The three most commonly used criteria are :

- **Visually clean. No residue visible on equipment after cleaning.**
- **No more than 10 ppm of one product will appear in another product .**
- **No more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.** **- Supplementary Training Modules on Good Manufacturing Practice, Cleaning Validation, World Health Organization, Feb 2009, Kampala, Uganda**

Risk Based Acceptance Criteria (Mollah & White)

- Maximum allowable carryover (MACO) and safety factors
- Process risk versus patient risk
- Manufacturing stage (pre, post, and during purification)
- Cross-contamination between products or product intermediates
- Single vial concept and worst-case cleaning

Examples of Cleaning Limit Criteria Calculation Examples - 1

Visually clean -

Spiking studies determine the concentration at which most active ingredients are visible

"A typical visual limit is NLT 4 µg / cm^2."

"Visually clean" may not be adequate in the case of

- Potent drugs
- Microbial contamination
- Endotoxin

Suitable for swab sample and not for rinse sample
More suitable for non-potent drug products and APIs.

N.B. PIC/S advocates spiked coupon study for determination of visual inspection limits (and for training of inspectors).

Examples of Cleaning Limit Criteria Calculation Examples - 2

Presence of no more than 10 ppm (mg/L, ug/ml) of the contaminant present in the product

Widely accepted cGMP technique.

$A = 10 \times MBS_{SUBS}$

Where:
A = Maximum acceptable mass of contaminant in subsequent product
10 = Limit of acceptance of 10 ug/mL
MBS_{SUBS} = Minimum size of the subsequent batch (g or mL)

Examples of Cleaning Limit Criteria Calculation Examples - 3

Maximum acceptable limit (µg) of contaminant in subsequent product

$MACO = (MTD_{CONT} \times MBS_{SUBS}) / (SF \times MAXTD_{SUBS})$

Where: SF = Safety factor (injectables 1000 – 10000)

MTD_{CONT} = Minimum therapeutic daily dose of the contaminant
MBS_{SUBS} = Minimum size of the subsequent batch (g or mL)
$MAXTD_{SUBS}$ = Maximum therapeutic daily dose in next batch (g or mL).

If MTD_{CONT} is unknown, No Observed Effect Level expression (NOEL) can be used to replace "0.0001 x MTD_{CONT}" above
NOEL = (LD50 X 70) / 2000
70 = Average weight of an adult person (kg)
2000 = Empirical constant.

Now calculation is

$MACO = [\{(LD50 \times 70) / 2000) \times MBS_{SUBS}\} / MAXTD_{SUBS}]$

Examples of Cleaning Limit Criteria
Sample Calculation for 1ml dose

Maximum Allowable Carry-Over (MACO) contaminant in next batch

MACO = (MTD_{CONT} x MBS_{SUBS}) / (SF x $MAXTD_{SUBS}$)

Therapeutic dose @ 7 mg/mL = 7mg

SF = 1000 (worst case parenteral)

Contaminant in single 1ml dose = MTD_{CONT} = 10ppm /ml = 10ug = 0.01 mg

Batch size of subsequent product (**MBS_{SUBS}**) = 100 L = 100,000,000 mg

Contaminant mass carried over ~= 150 mg

Working backwards to an "acceptable limit"

What is the rinse limit after we CIP for A prior to making a batch of B?

Final Post batch CIP rinse = 100 L

150 mg / 100L = 1.5 mg/L (1.5 ppm) of contaminant in the post CIP rinse sample

Comment on TTC (Threshhold of Toxicological Concern)

Toxicology assumes that all contaminants are genotoxic (cancer forming)

Vaccines are a special case of an injectable products and are very different to many pharmaceutical products

European Vaccine Manufacturers “reflection paper on the Safety Assessment of Residuals and Contaminants in Vaccines”

The paper provides background information and an overview of the existing regulatory framework, which can be used as a basis to formulate a general approach for the safety assessment of residuals and contaminants in vaccines.

Duration Of Treatment	Single Dose	≤ 1 month	≤ 3 months	≤ 6 months	≤ 12 months	> 12 Months
µg/day	120	60	20	10	5	1.5

This helps determine acceptable TOC concentration at the final dose and in the final vessel

Example of Cleaning Multiproduct Equipment
Processing tank used for Hib and Meningitis A & C

- Hib determined as worst case based on formulation solubility
- Shortest rinsing time (5 mins), fewer rinses than in standard production. longest time between end of batch and start of cleaning (72 hours)
- Three runs conducted at +/- 0.1 pH unit from process set point (5.7 pH)
- Product recovery steps done for rinse & swab methods

Shows that cleaning is effective in	worst case conditions
WFI rinse after 72 hrs (endotoxin)	> 250 EU/mL
B Visible residues	No
Post CIP Final Rinse Water (TOC, cond, pH)	TOC: 0.0183 ug/mL, Cond.:0.914uS/cm, pH: 5.5
Post CIP Final Rinse Water (endotoxin)	< 0.250 EU/mL
Max Clean Hold Time Final Rinse Water (TOC, cond, pH)	TOC: 0.0286 ug/mL, Cond.:0.797uS/cm, pH: 5.6
Max Clean Hold Time Final Rinse Water (endotoxin)	< 0.250 EU/mL

- **Cleaning validation of a multipurpose tank used for Type b haemophilus influenzae and meningitis a and c Vaccine formulation" Bago et al. 2012**

Points to note on cleaning validation

- **Hold times**

  Validation must be done on the worst case scenario. This is particularly critical for processes that have variable hold times after processing before cleaning

- **Feed variability**

  The most contaminated feed with maximum product must be analysed

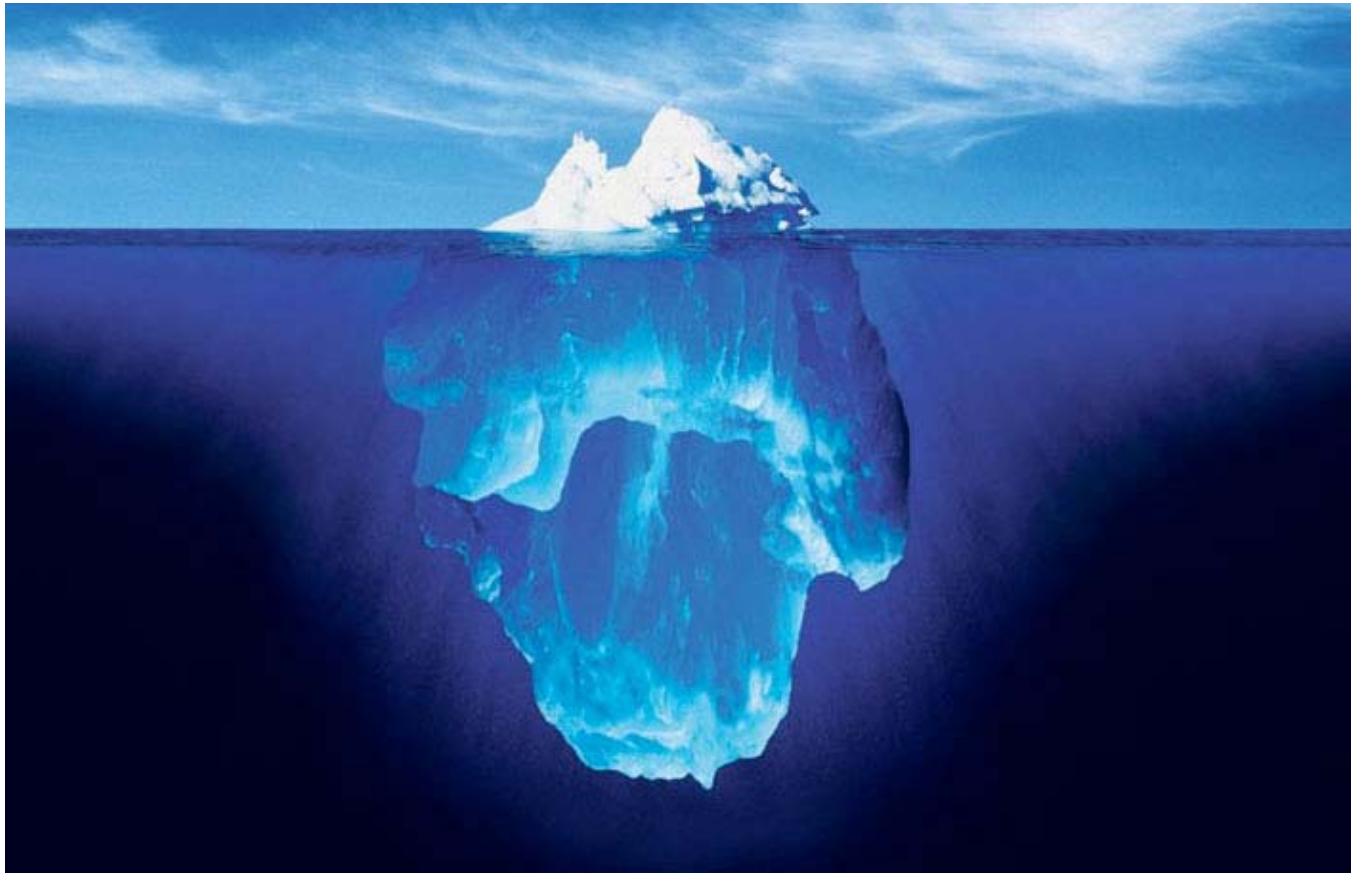
- **Grabs and timepoints**

  Take samples throughout the cleaning cycle. A too long cleaning cycle can produce as many problems as a too short one.

Cleaning Validation Summary

- Cleaning Validation promotes product and patient safety.
- Need to use multiple sampling methods
- Understanding product, process, critical attributes is vital
- Demonstrates that the cleaning process adequately and consistently removes product, process and environmental residues from the cleaned systems so they can be used for the manufacture of subsequent products.
- Can be aligned to a validation lifecycle approach that encompasses development, qualification and validation phases.
- Supports process improvement and innovation through sound science.
- Grouping Strategy (Matrixing, Bracketing) is a risk based approach to CV that reduces the validation workload, while maintaining assurance that the acceptance criteria are met.

Thank You for your Attention!
May we be of Further Assistance?



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WHO Expert Committee On Specifications For Pharmaceutical Preparations (especially Annex 3 – Cleaning Validation), TRS937, 2006.

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PICS Recommendations on Validation Master Plan Installation and Operational Qualification non-Sterile Process Validation, Cleaning Validation PI 006-3, Sept. 2007

PDA Points to Consider for Cleaning Validation, TR29 (revised 2012)

PDA Process Validation of Protein Manufacturing, TR42, Oct 2006

PDA Points to Consider for Biotechnology Cleaning Validation, TR49, 2010

APIC CEFIC Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants, Dec. 2000,

ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients,

PICS Guide To Good Manufacturing Practice For Medicinal Products
Annex 15 Qualification and Validation, PE 009-10 (Annexes) - January 201

Appendix 1 – 10ppm Calculation

Cleaning Validation Acceptance Criteria

10 PPM criteria :

Based on the hypothesis that 10 parts of previous product is therapeutically ineffective if presents in million parts of next product.

Step 1

Determination of MAC

$$MAC = \frac{10 \times BS}{1000000} \quad \textit{(unit of mass)}$$

Where, **BS = batch size (smallest available batch size)**

Then use **Step 2** and **Step 3** to derive final swab residue limit.

Cleaning Validation Acceptance Criteria

10 PPM criteria (an example) :

Step 1

Determination of **MAC**

$$\text{MAC} = \frac{10 \times 150\ \text{kg} \times 1000000}{1000000} = 1500\ \text{mg}$$

The final **Swab residue (L_2) :**

$$\frac{1500\ \text{mg} \times 25\ \text{cm}^2}{3170\ \text{cm}^2} = 11.83\ \text{mg/swab}$$

Cleaning Validation Acceptance Criteria

Step 2

Therapeutic dose based criteria (an example) :

Determination ~~of~~ **~~Surface~~ contamination level**

$$= \frac{\textbf{2000 mg}}{\textbf{3170 cm}^2} = \textbf{0.63 mg / cm}^2 \quad (L_1 \text{ value})$$

Cleaning Validation Acceptance Criteria

Therapeutic dose based criteria (an example) :

Step 3

Determination of **Swab residue**

0.63 mg / cm^2 × 25 cm^2

= **15.75 mg / swab** (L_2 value)

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