Current Trends in Cleaning Validation

Beth Kroeger, STERIS Technical Services Manager
Beth_Kroeger@steris.com

Agenda

- Rings on Buffer and Media Tanks
- Health based limits
- FDA Trends
- Process Understanding

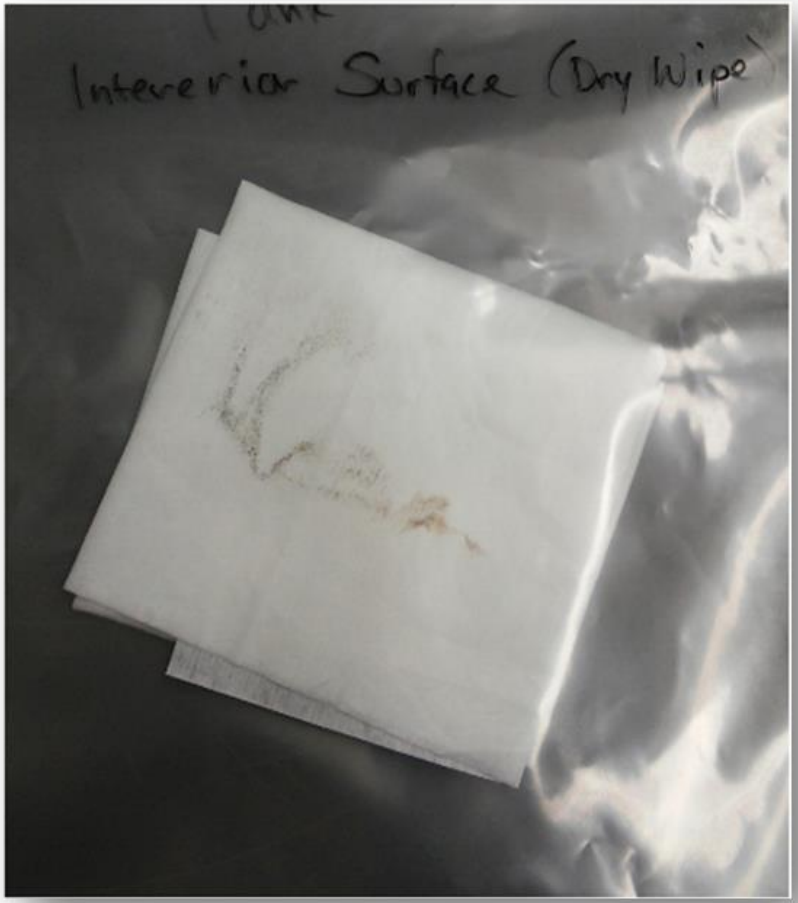
Is this clean?

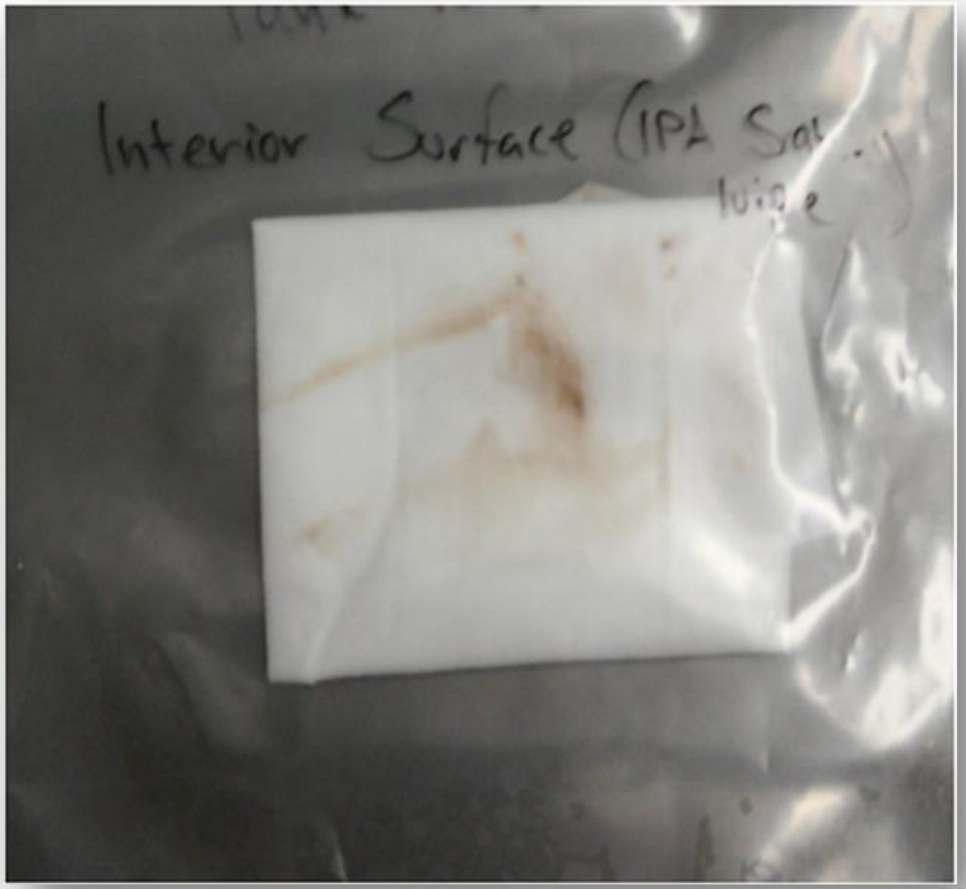
Initial Incident Discovery

WFI System Distribution Loop Roughing Discovered in Buffer Prep

- Tech found red from AWFI rinse residue dripping on white sterile wipe
- Roughing source investigation discovered “faint black rings” in buffer prep vessels when additional lighting and closer visual inspection was applied in MAR16. The three 600L vessels had darker rings than the less frequently used 100L vessel.
- Red roughing found upstream at AWFI source in piping.
- 30 min of citric acid manual scrubbing followed by three hot WFI rinse cycles performed. pH and conductivity rinse found to be neutral (within WFI specs). Improved slightly per visual inspection but white sterile wipes didn’t remove black residue anymore. COP of the 100L proved to get it visibly clean.
- Since MAR16, BAM monitoring using sterile wipe for black residue accumulation. Rings still seen in 600L vessels though.
- Non-Conformance closed by QA in APR16. CAPAs issued for improved tank visual inspection, modification of cleaning procedures, and passivation of the four vessels.
- Sat. & Sun. 16th & 17th of JUL16, vessels passivated in BAM room by Plant Maintenance Services. Post results changed little; rings can still be seen in the 600L vessels.

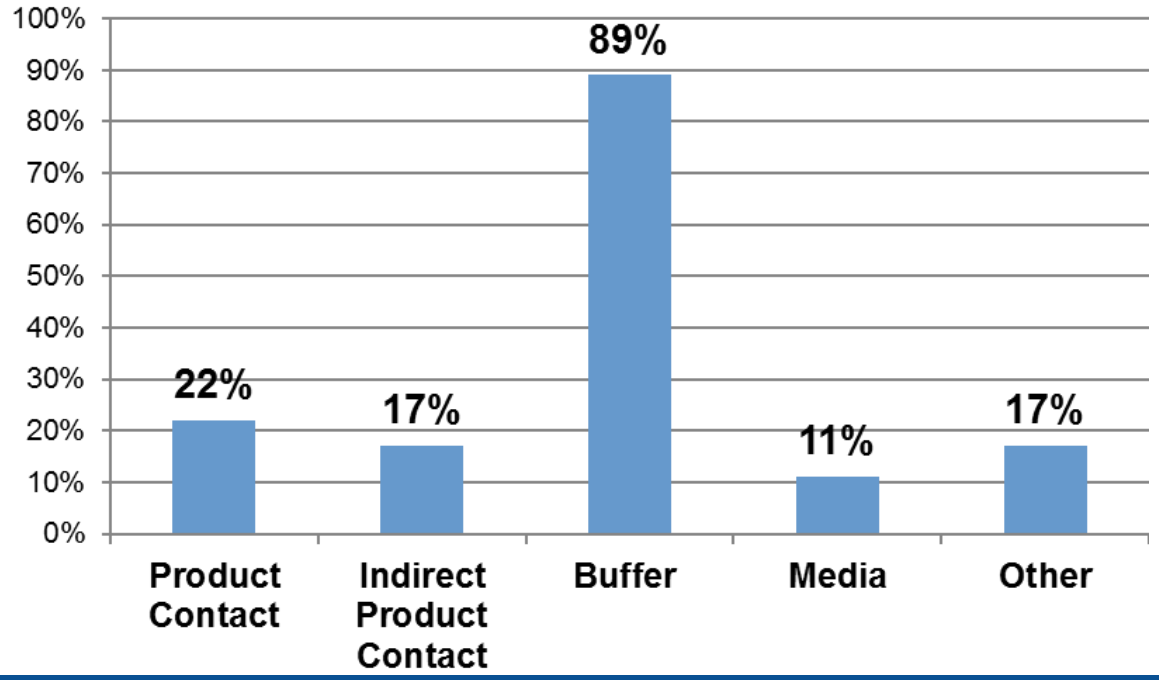
Is this clean?





Recent Survey

- CIP Technology and Industry Benchmarking Summit in Longmont CO
- Question 22: Do you use water on CIPs? **90% Yes, 10% No**
- If Yes, for what equipment?



What frequency?

89% between batches of same product

44% between batches of different product

2% Other

Background

- Cleaning processes are designed based on
  - nature of the soil
  - condition of the soil
  - surface material
  - cleaning factors
- ALI rings can be challenging to clean
- This is not a new issue however the subject has received a lot of attention recently

Industry Articles

Downloaded from journal.pda.org on June 30, 2016

PDA Journal of Pharmaceutical Science and Technology

Investigation of Air–Liquid Interface Rings in Buffer Preparation Vessels: the Role of Slip Agents

Ting Shi, Wei Ding, Donald W. Kessler, et al.

PDA J Pharm Sci and Tech 2016 70 272-281
Access the most recent version at doi: 10.5731/pdajpst.2015.005736

Technical Articles

FACILITIES AND EQUIPMENT

Cleaning Buffer Preparation Tank Air–Liquid Interface Rings

Buffers are routinely used in biopharmaceutical manufacturing operations to adjust pH, salinity, or nutrient levels; equilibrate and flush columns and filter membranes; and for in-process and final product formulations. While buffers are easily cleaned with water (with a few exceptions due to high water solubility), the industry continues to struggle with visible residue at the air–liquid interface on buffer preparation and storage tanks. The residue can adhere tightly to the surface, appearing as distinct bands or rings at the air–liquid interface. Articles and presentations have been published that define the residue as hydrophobic in nature and due to trace polymers from the packaging, handling, raw materials, or manufacturing processes found in buffer components.[1] These trace components, such as slip agents, are used to help the flow of dry ingredients, manipulation of plastic packaging, and storage of the components. Hydrophobic components can also be derived from worn or chemically incompatible gaskets, valve diaphragms, and tubing materials.

This article will review the different types of buffers, provide approaches to investigate the best cleaning procedure using laboratory testing, and detail strategies for cleaning air–liquid interface residues within buffer preparation and storage tanks.

Buffer types

Buffers are solutions whose pH is altered not to any great extent by the addition of small quantities of strong acid or strong base. Buffer solutions are divided into two types:

1. Acidic buffers are a mixture of a weak acid and a strong base, for example acetic acid (CH_3COOH) and sodium acetate (CH_3COONa). A solution containing equal quantities of acetic acid and sodium acetate maintains a pH value around 4.75.

$$pH = pK_a + \log(\text{salt/acid})$$

where K_a is the acid dissociation constant of the weak acid.

2. Basic buffers are a mixture of a salt of a weak base and a strong acid, such as ammonium hydroxide (NH_4OH) and ammonium chloride (NH_4Cl). A solution containing equal parts of this of ammonium hydroxide and ammonium chloride maintains its pH value around 9.25.

$$pOH = pK_b + \log(\text{salt/base})$$

where K_b is the base dissociation constant of the weak base. These equations are called Henderson–Hasselbalch equations.

Buffers can be further divided:

- Single-substances solutions, which represent the solutions of the salt of a weak acid and weak base.
- Mixture solutions, which represent any acid buffer or basic buffer.
- Natural buffers solutions, which maintain the pH within a variety of conditions. Human blood, for example maintains a pH values around 7.35 in spite of the wide variety of foods we consume.

Buffer solubility

Buffers are generally cleaned with water (with some exceptions, such as human blood), based on their solubility in water. Look A lists buffers and their solubility in water[2-5]

Nonroutine cleaning challenges

Common challenges with cleaning buffer preparation tanks are the bands of residue found along air–liquid interfaces. These can occur after a single production batch or multiple batches of the same or differing buffers. As reported in the 2013 CIP Summit[6] benchmarking survey, 89% of the participating companies that use water for cleaning reported that their buffer preparation tanks were cleaned with purified water. Buffer pH solubility supports the use of "water-only" cleanings, but companies continue to be challenged with visible residue on the preparation tanks commonly referred as bands or rings.

Common approaches to cleanings air–liquid interface rings[7-9]

- Increased spray impingement by using rotating spray devices focused on the air–liquid interface
- Increased time of the initial rinse, which typically removes gross residue
- Use of oxidizing agent with an alkaline cleaning solution
- Increased temperature (25–63°C)
- Use of a formulated cleaning agent containing surfactants and chelants
- Increased cleaning agent concentration
- Clean first with an acid, followed by an alkaline cleaning agent

Laboratory testing model

Laboratory testing has been effective at defining critical cleaning parameters for removing process residues.[7,8] Laboratory testing involves applying the residue on a surface that is representative of the preparation and storage tank. The test continues by conditioning the soiled residue on a surface to simulate the "real-world" process, and finally cleaning the surface in a manner that is representative of how the equipment is normally

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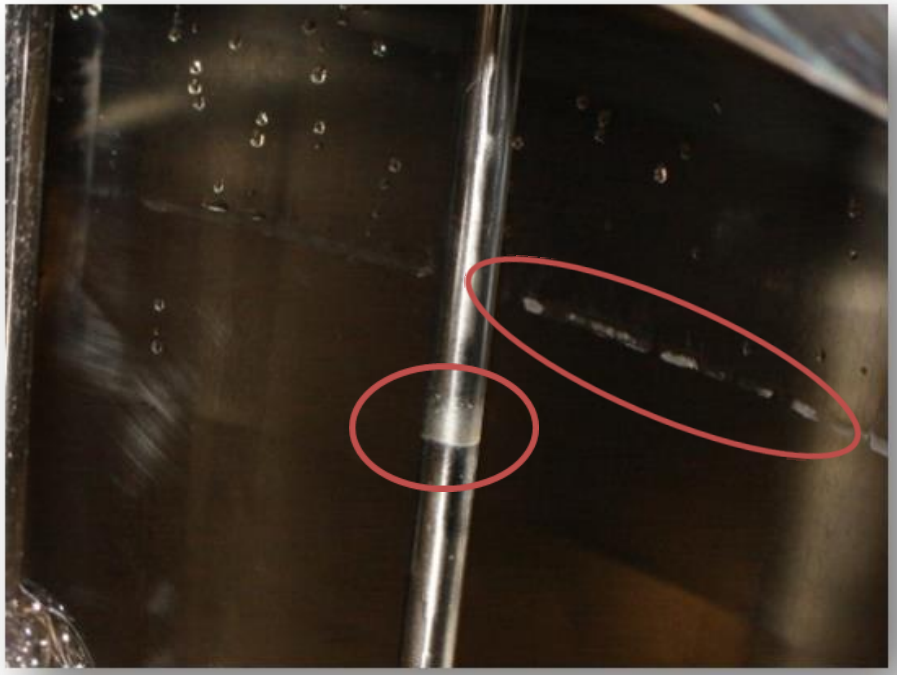
Air-Liquid Interface Residues

- Trace elements are normally at ppb levels
- Normally hydrophobic and migrate to surface
- High mixing speeds assist with migration to surface and adherence to side walls
- Large liquid volumes increase trace residues present
- Small surface area at ALI allows concentration of residues at ALI
- Hot water rinses can heat surface and bake residues onto side walls

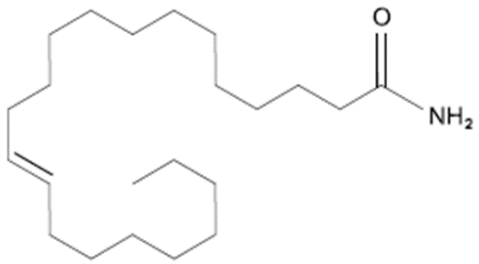
Example of rings in buffer tanks



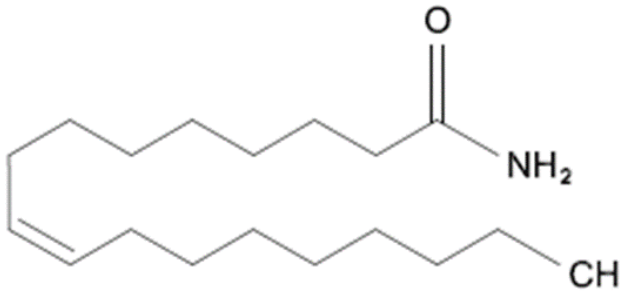
Air-Liquid Interface Residues

- Raw material impurities
  - Hydrocarbons (Steramide, Erucamide, Oleamide)
    - Mold release agents used in processing of bags & and equipment
    - Prevents caking of powders
    - Found on bags used for storage and transport
  - Polymers (Teflon, Nylon, PTFE, Silicone, etc.)
    - Equipment used in raw material manufacturing
    - Bags or containers used for raw material storage
    - Impurities from source material
  - Mineral Silicates (anti-blocks) (Silica, Talc, Kaolin)
  - Lubricants
  - Valves, gaskets and tubing – (source for siloxanes)

Slip Agents



Erucamide



Stearamide

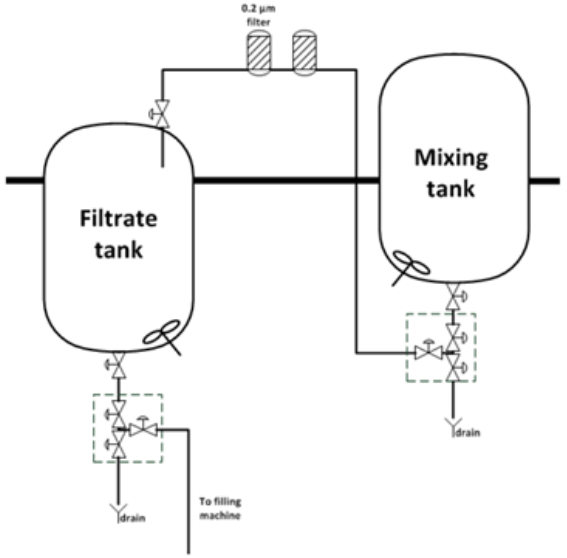
- Insoluble in water and buffers
- High melting points
- Comprised of fatty acid derivatives and also insoluble salts
- Tend to float at the liquid surface & aggregate at air-liquid interface
- Deposit on side walls of tanks
  - Or are baked on side walls of hot surface

Industry Awareness

- Raw materials used in buffer solutions are stored and transported in bins lined with plastic bags or in the raw materials themselves.
- Plastic bags (poly liners) are manufactured from films made by extrusion for a range of purposes and industries.
- Slip and anti-block additives are added to resins to promote slip between the layers of the film to reduce friction and ‘tackiness’ to increase the ability of the material to slide over itself
- **Unintended consequence: trace amounts mix with the materials stored in the plastics liners and subsequently appear in bioprocess preparation tanks.**

Filtration of slip agents

- Filtration studies show that slip agents do not pass through filters
  - Exception could be for detergent based buffers for example S/D buffers
  - Recently seen at Customer site where compounding tank has issue with rings and filtrate tank does not



Industry Awareness

- Set specification in user requirement definitions for suppliers to remove from material/processes
  - Benchmarking showed that specifying ‘no slip agents’ was not customary.
- Research showed that low-density polyethylene and linear low-density polyethylene liners are the most frequently used liners in packaging raw materials. Many grades include the use of slip and anti-block agents but some grades do not.

What the raw material vendors do

- How do bag and slip agent manufacturers clean their own equipment?
  - Solvents
    - Involve manual wipe down
    - Flammable
    - Not suited for CIP of pharma & biopharma equipment
- Key is to dissolve hydrophobic residues in aqueous solutions

Common Cleaning Approaches

- Increase spray impingement by using rotating spray device
- Increase temperature of cleaning (75-85C)
- Use of formulated cleaning agent
- Increase cleaning agent concentration
- Use of an oxidizing cleaning agent or detergent additive with an alkaline cleaning solution
  - Keep temp > 50° C to < 65° C
- Formulated alkaline detergent alone or in combination with a formulated oxidative detergent or surfactant based detergents.

Example: ALI Rings in Biopharm process

MAB MFG using attached mammalian cells culture

Soil	Cleaner	Conc.	Method	Temp	Time
Media	Formulated Alkaline Detergent	1% v/v	AI	60 C	15 min.
Cell Culture	Formulated Alkaline Detergent	1% v/v	AI	60 C	30 min
A/L Residue	Formulated Alkaline Detergent	4% v/v	SW	80 C	1-4 hrs*

- The brown ALI residue pictured was cleaned using 1% formulated alkaline detergent at 80C in 15 minutes.
- **A faint white ALI residue required increased action, temperature and cleaning time**

Example of recommended cleaning frequency

- Group 1: Very High: Halide Salt Buffers > 5M: Clean & **Passivate after every formulation**
- Group 2: High: Halide Salt Buffers 2 – 5M: Clean & Passivate after every **10** formulations
- Group 3: Moderate: Halide Salt Buffers 1 to 1.5M: Clean & Passivate after every **20** formulations
- Group 4: Low: Halide Salt Buffers 0.1 to 1M: Clean & Passivate after every **50** formulations
- Group 5: Very Low: Halide Salt Buffers <0.1M: Clean & Passivate after every **100** formulations

Risk model example provided by Josh Anthes, Patheon and Beth Kroeger, STERIS Corp

Conclusions

- Identify components of the ring
- Determine whether intrinsic or extrinsic to process
  - Intrinsic: modify cleaning procedure
  - Extrinsic: try to eliminate source or modify cleaning procedure
- PACE evaluation can be a tool to assist in the investigation or corrective action
- Risk assessment should be performed
- Visible residues may need to be manually cleaned
- **Routine cleaning with a formulated cleaning agent containing surfactants at elevated temperature may prevent visible residue buildup and avoid manual cleaning**

Agenda

- Rings on Buffer and Media Tanks
- Health based limits
- FDA Trends
- Process Understanding

What is cleaning for?

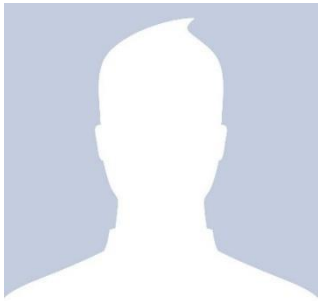
- Cleaning has to do with what is manufactured **next**
- Need information for **subsequent** product:
  - Formulation
  - Dosing
  - Route of administration
  - Batch size
  - Shared equipment
  - Product specifications (for bioburden and LAL specs)

The Basis for Quantitative Limits

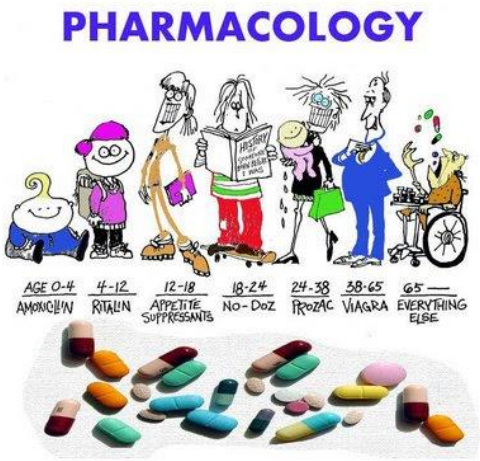
- Limits are usually based on one of the following:

Toxicity of the residue based on NOAEL

A default value



MAC = $\frac{\text{MDD x 0.001}}{\text{LDD}}$ x max batch



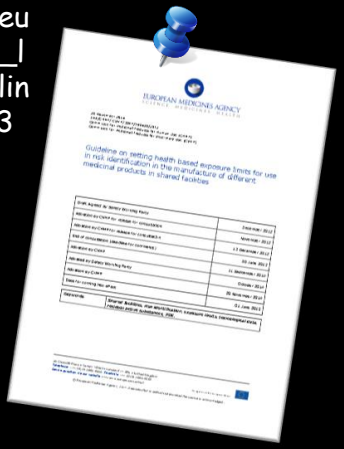
Health based limits

ADI = LD50 (mg/kg) × body weight (kg)/10^5

NOEL = LD50 (mg/kg) × (5.6×10^{-4}) x 70 kg

Limits Timeline

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177735.pdf



EMA: Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, Published: November, 2014

Fourman, G., and Mullin, M., "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations," Pharmaceutical Technology, April 1993

EMA: Guideline on setting health based exposure limits Effective date: June 2015

Effective for new product: December 2015

1990's

2000

2010

2015

2016

FDA Guidance: Guide to Inspections Validation of Cleaning Processes, July 1993

PDA Technical Report No. 29 "Points to Consider for Cleaning Validation". 1998 Revised: 2012

ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP), September, 2010

EU GMP Annex 15: Qualification and Validation, Section 10 Cleaning Validation Effective: October 2015

Effective for existing products: June 2016

Health based Limits

- ISPE Risk MaPP and recent EMA document are two main advocates & EU GMP Annex 15
  - ADE: Acceptable daily exposure
  - PDE: Permitted daily exposure
- Refers to limits based on **toxicological** evaluation
  - Focuses on **how** carryover might cause harm.
  - Value represents dose that is unlikely to cause an adverse effect if an individual is exposed at this dose every day for a lifetime

Health based Limits

- Why?
  - Some felt that “traditional” method was not “risk-based”
  - Use of 1/1000th daily dose of active seen by some to be “arbitrary”
  - Some questioned the use of 10 ppm as the “default” value as arbitrary and possibly not reflective of potential risks
  - Current approach could lead to either overly prescriptive limits or inadequate limits

Health based Limits

$$\text{ADE (mg/day)} = \frac{\text{NOAEL} \times \text{BW}}{\text{UF}_C \times \text{MF} \times \text{PK}}$$

- Where:
  - BW = Body weight
  - UF_c = Composite uncertainty factor
  - MF = Modifying factor
  - PK = Pharmacokinetic adjustments (route to route adjustments)
- **No other safety factors applied.**

Health based Limits

$$\text{ADE} \times \frac{\text{Batch Size}}{\text{Maximum Daily Dose}} = \text{STV}$$

- Rather than:

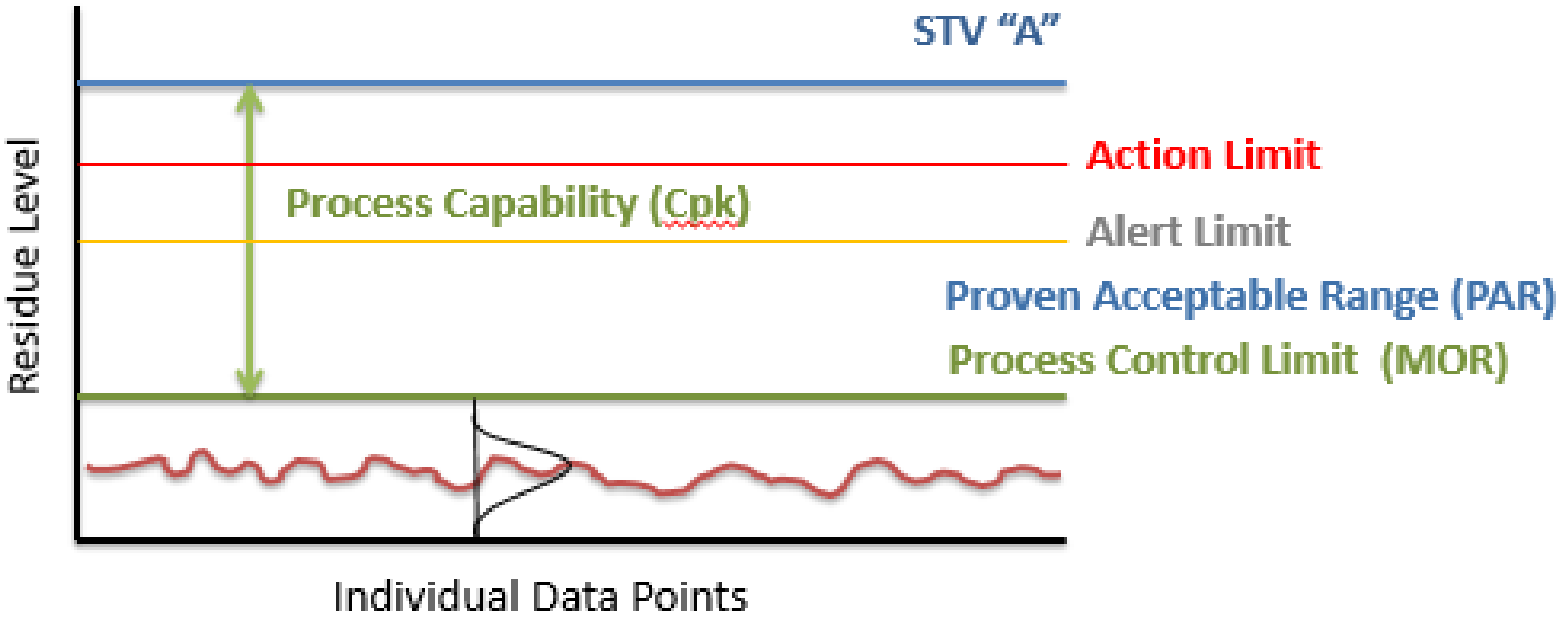
$$\frac{\text{Minimum Therapeutic Dose} \times \text{Batch Size}}{\text{Maximum Daily Dose}} \times \frac{1}{\text{Safety Factor}} = \text{MACO}$$

Calculation of ADE Value

- Per ISPE Baseline®Guide: Risk-Based MaPP
  - ADE should not be seen as a “limit”
    - Initial acceptance criteria are limits safe for the patient
  - Use as a reference point for determining level of risk
  - Establish Process Control Limits based on PD Studies
    - Tighter inner control limits (MOR’s & PAR’s)
    - Calculated per statistical analysis of CV data and monitoring data
- ADE limit alone may not be acceptable as carryover, though considered safe
  - Flavor, smell, product quality, etc.
  - Default to visually clean

Health based Limits

- The STV should be used with the process capability of the cleaning process to establish the alert and action levels:



Issues

- Several critical effects identified resulting in the calculation of more than one PDE value:
  - Use lowest PDE value
- Two (or more) different values from different Toxicologists:
  - Use lowest PDE value
- Rationale for having some check on an ADE/PDE only approach
  - **NOTE: FDA has questioned this with respect to process control capabilities.**

Issues with Biologics due to denaturation

- EMA "Guideline on setting health based limits…" 20 Nov 14
  - Section 5.3 "In view of this, the determination of health based exposure limits using PDE limits of the active and intact product **may not be required**.
- EudraLex, Volume 4, "EU Guidelines for GMP for Medicinal Products…Annex 15: 30 Mar 15
  - Section 10.6.1: "Therapeutic macromolecules…known to degrade and denature when exposed to pH extremes and/or heat…**A toxicological evaluation may therefore not be applicable…"**

Issues with Biologics due to denaturation

- Active is degraded after cleaning
  - Irrational to use product specific assays
- Acceptance limits often below LOD of non-specific methods
  - Large surface areas/small batches/low doses

Biologics rational using WFI specifications

- Equipment can not be cleaner than the last solution to contact surface
  - Last solution WFI
  - WFI specification ≤ 500 ppb TOC
  - ~ amount of carbon in protein is 50%
- Maximum Surface Residual TOC (ng TOC/cm^2) =

$$\text{Max surface TOC} = \frac{\text{Equipment volume (mL)} \times \text{WFI limit (ng TOC/mL)}}{\text{Equipment Surface Area (cm2)}}$$

Biologics rational using Toxicology

- Denatured biopharmaceutical product fragments may be considered to be Class 1 chemicals with a residual soil threshold of 100 µg/day

Acceptable Residual Limit (ARL) (µg/cm^2)

$$= \frac{100\ \mu g/day \times \text{minimum batch size (mg)}}{\text{Dose (mg/day)} \times \text{surface area (cm}^2\text{)}}$$

Residual TOC Swab Limit (µg TOC/swab)

= Acceptable Residual Limit (µg/cm^2) x SSA (cm^2/swab) x 50%

Where the approximate amount of carbon in protein is 50%

Reference: JVT 2013 Vol 19, number 4, *Methodology for Assessing Product Inactivation During Cleaning Part II: Setting Acceptance Limits of Biopharmaceutical Product Carryover for Equipment Cleaning*

Limits based on thresholds

- Regulatory Toxicology and Pharmacology 43 (2005) 1-9, Dolan, D., Naumann, B., *Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations*.
  - ADI recommendations based on threshold values for resolution of atypical extraneous matter investigations
    - Carcinogens: 1µg/day
    - Unstudied compounds with limited data: 10 µg/day
    - Compounds not likely potent, highly toxic or carcinogenic: 100 µg/day

Slip agent ring, acceptable limit and defending to FDA

Tank XX Calculations

$$Height = 237.38\ in$$

$$Diameter = 120\ in$$

$$Surface\ Area = \pi * D * h = \quad * 25\%\ tank\ ring$$
$$= \quad in^2\ of\ ring\ material$$

$$in^2 = \quad m^2 * 0.0001\ m\ (thickness\ of\ A4\ paper) = \quad m^3$$

Assuming the ring material is made of polyethylene,

because it has the lowest density of the ring materials, at $920{,}000\ \frac{g}{m^3}$

$$m^3 * 920{,}000\ \frac{g}{m^3} = \quad 8\ g\ ring\ material\ at\ 25\%\ surface\ of\ tank$$

If 1.5% *dissociates into the solution*

$$\frac{g\ ring\ material}{nL\ smallest\ batch\ size} * 0.015$$
$$= 1.327x\ 10^{-6}\ \frac{g}{mL}\ or\ concentration\ of\ ring\ material\ in\ smallest\ batch\ on\ this\ tank$$

Largest daily dose of Tank XX products is $\quad mL$

$$2{,}400\ \frac{mL}{day} * 1.327\ x\ 10^{-6}\ \frac{g}{mL} = \quad \frac{g}{day}$$

$$\frac{\mu g}{day}\ of\ ring\ material\ exposed\ to\ a\ patient$$

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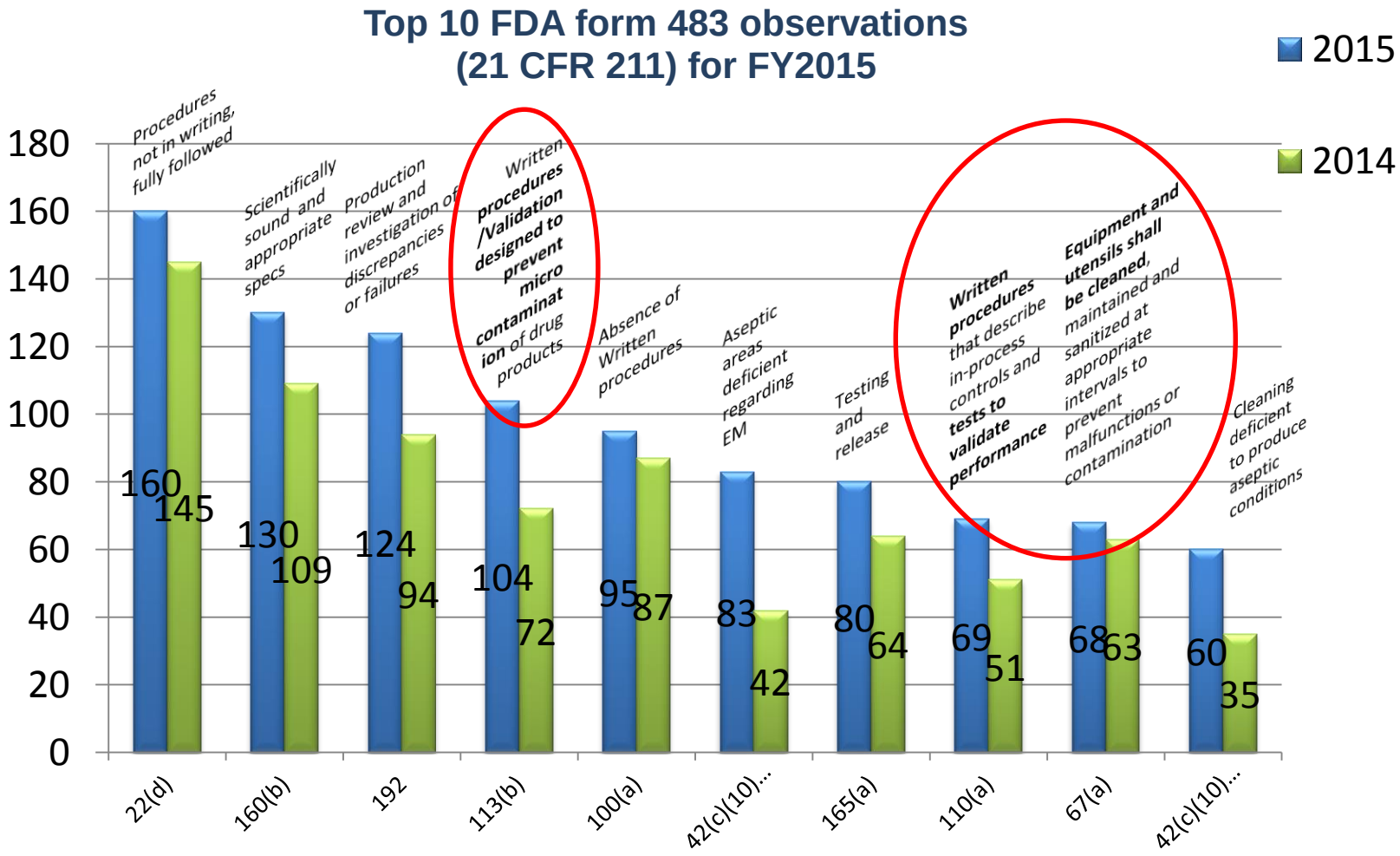
FDA Strategic Priorities

- FDA has indicated that the following areas are (GMP) inspectional priorities: (risk based inspection program)
  - High risk products
  - Prescription drug manufacturers
  - Sterile drug manufacturers
  - New facilities not yet inspected
- Important priorities
  - Assessment of “Breakthrough Therapies” program
  - Expedited review programs

Janet Woodcock
Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA)

Most Frequent form 483 observations – FY2015



Information from FDA website: http://www.fda.gov/ICECI/Inspections/ucm424098.htm

Agencies focusing on Cleaning Validation

- 15% of all observations (483's) related to cleaning validation and documentation

Why a sound cleaning program is important?

- Cleaning shows an Auditor a lot about a facility
  - Quality mindset – How site makes decisions under manufacturing schedule stress (first patient in)
  - How they investigate deviations
  - Do they understand the process?

Inspection focus

"There is not sufficient documentation to determine the effectiveness of your cleaning [process]".

Cleaning Agent Selection Study

"You have not established adequate rationale for determining this product as the most difficult product to clean".

Worst Case Residue Study

"For example, your firm does not have data to demonstrate cleaning process for non-dedicated manufacturing equipment and utensils are adequate".

Cleaning Process Design Space Studies

Cleaning Agent Selection Study

Agenda

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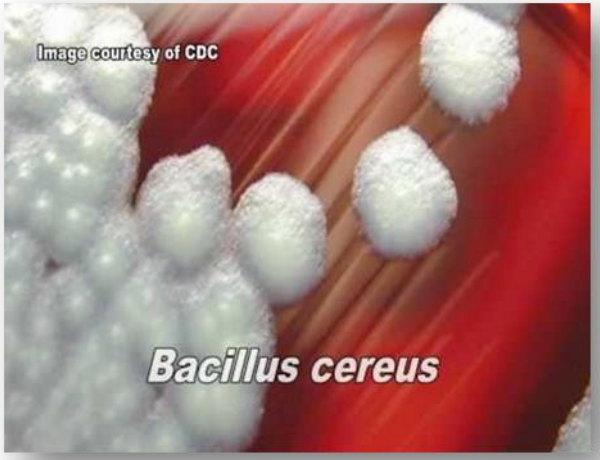
Do you understand your process?

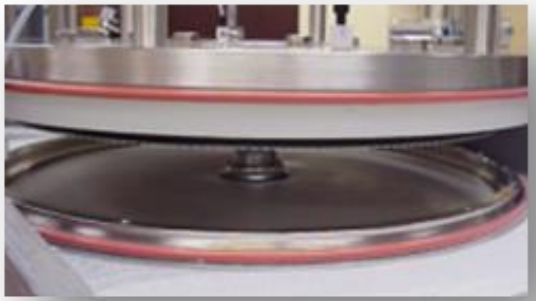
- Meet with your team or “Customer”
  - Discuss process residue details
    - Aqueous, oil based, suspension, solids, powders, etc
  - Equipment surface MOC
  - Available cleaning methodology options
  - Process temperature and process details
  - Decontamination step?
  - Dirty hold time
  - Restrictions?
    - Schedules, waste, limitations

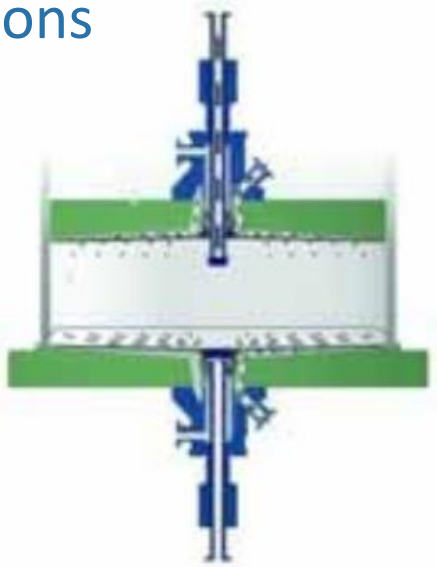
Bacillus cereus contamination in eluate



Bacillus cereus contamination in eluate

- Sporadic contamination of MabSelect Sure Protein A eluate with *b. cereus* (5 x 10L RA drug product contaminated)
- Removed pH probe during product charge
- Changed from static soak during sanitization to dynamic conditions in up-flow and downflow configurations





Bacillus cereus contamination in eluate

- Remove 2-port, 3-way ball valves used for column isolation during skid sanitization with 0.5 N NaOH
- Removed resin for remedial clean with guanidine HCL while stirring to ensure all of resin in contact with solution
- Walked through P&ID and validation
  - Increased flow rate for skid when column in by-pass
  - Turbulent flow >1.5 m/s

Bacillus cereus contamination in eluate

- Reviewed raw material specifications and Certificates of analysis of current lots in use

Certificate of Analysis

Product:
MabSelect SuRe™

Code Number:
17543805

Lot No: 10250908

Test/Characteristic:	Limits:	Results:
Breakthrough capacity, $Q_{B,10\,\%}$ mg human IgG / ml packed medium	min. 28	37
Microbial contamination Colony Forming Units / ml suspension	max. 100	0

In Conclusion….

- Building an effective cleaning program involves
  - Understanding your process
    - Equipment design considerations
    - Process considerations
  - Evaluation of soiling conditions
  - Establishing correct limits, both cleaning validation and incoming raw material specifications (or testing worse case for process capability)

Current Trends in Cleaning Validation

Beth Kroeger, STERIS Technical Services Manager
Beth_Kroeger@steris.com