The Life Cycle Approach to Cleaning Validation

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Life Sciences



Presented By:

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August 2014

Science & Solutions for Life

Agenda

7:30 – 8:30	Registration
10:30 – 10:45	Break
12:30 –13:30	Lunch
15:30- 15:45	Break

Note: Please refer to the seminar brief for topic list



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An Introduction to Cleaning Validation for the 21st Century

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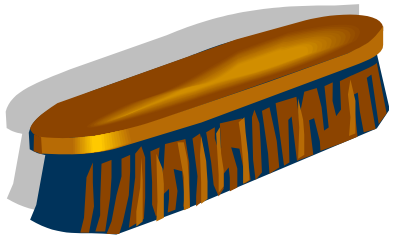
Cleaning

- Definition: The process of removing potential contaminants from process equipment and maintaining the condition of equipment such that the equipment can be safely used for subsequent product manufacture.
- Need to consider cleaning, sanitizing (if performed as separate step), storage.

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Why clean?

- Product integrity
  - Cross-contamination
  - Microbial integrity
  - Other chemical species
  - Lot integrity
- Equipment reuse
- Regulatory compliance



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Cleaning validation

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- Different from process validation
- Involves “intersection” of two products
  - Product just manufactured- good cleaning to remove residues to acceptable level
  - Product subsequently manufactured- residue levels based on possible contamination of this product
- Must always evaluate effects on subsequently manufactured product
- Typically CV has own master plan/policy



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Cleaning validation



- Documented evidence (reports)
- High degree of assurance (data)
- Consistency (*traditionally* 3 PQ runs)
- Predetermined quality attributes (of equipment)

➡For repeated cleaning processes

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What validation applies to?

- *Critical* cleaning must be validated
  - Cleaning between different products
  - Focus on product contact surfaces
  - Applies to drug products and APIs
- Not required for *non-critical* cleaning
  - Floors, walls, outside of vessels
  - Some intermediate steps (ICH Q7)
- Others
  - Significant *indirect* product contact surfaces
  - Dedicated equipment



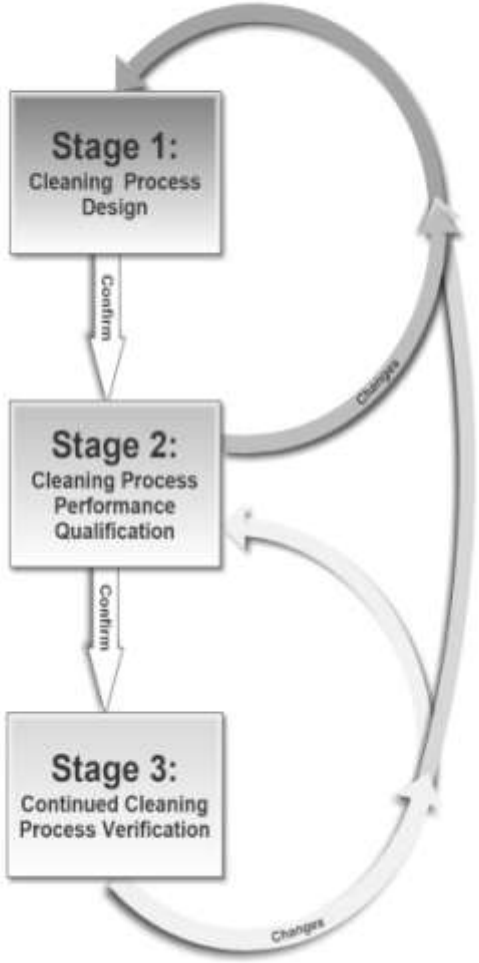
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Traditional vs. new direction

- Traditional
  - Qualification runs at commercial scale
  - PQ is minimum of 3 validation runs
- New direction
  - US FDA Process Validation Guidance (2011)
  - Validation is everything done (throughout life cycle) to assure effectiveness of process
  - Does not specify number of runs in a validation protocol

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Lifecycle Stages



- Three stages
  - 1: Design (includes development)
  - 2: Qualification (protocols)
  - 3: Continued process verification (validation maintenance, ongoing process verification, ongoing process control)

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Emphasis: risk based

- Assessment of risks based on *understanding* of cleaning process
- Focus on those issues that have potential major impact on product quality and patient safety
- Requires:
  - More “upfront” work
  - Multi-disciplinary input
- Note: Most risk documents focus appropriately on patient risk. However, need to also consider business risk.



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Consequences

- Support for effectiveness can be laboratory, scale-up and commercial runs
- More open to support from studies on similar processes
- May add flexibility, but is a *major paradigm change*



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Application to Cleaning?

- The FDA document *formally* applies to PV (although draft Annex 15 might apply to CV)
- Approach of many is to apply *principles* of lifecycle validation to cleaning process
  - Cleaning is just a special type of process



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Difference?

- One major focus of *process validation* is quality *within a batch* and *from batch to batch*
- For cleaning validation, are not expecting residues to be the *same* between batches
  - Key is whether they are *below* acceptance criteria
- Be careful of applying statistical principles where they are not applicable and/or they are not helpful



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Second Difference?

- Second important difference:
  - For the most part, each product manufacturing process is *unique*
  - For the most part, a manufacturer will use the *same* cleaning process for a given equipment item regardless of which product is manufactured
- Affects relevant *knowledge base* for new products significantly
- Allows grouping/matrixing



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Cleaning verification?

- For unique / non-repeatable events
  - clinical products, infrequent production, maintenance, deviations
- Documented evidence
- High degree of assurance
- Quality attributes may be evaluated later depending on next product



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Stage 1: Process Design

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Aspects to consider in the selection of cleaning agent and method

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Cleaning process design

- Key elements to be considered in design
  - Equipment to be cleaned
  - Soils to be removed
  - Cleaning methods
  - Cleaning agents
  - Cleaning mechanisms
  - Cleaning parameters
  - Residue limits



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Equipment

- Type and design?
  - Difficult to clean locations
  - Is selection of cleaning method limited?
  - Legacy systems for CIP?
- Materials of construction?
  - Important for selection of cleaning agents and parameters
- Clean individually or as train



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Soils

- Actives, excipients, process materials, bioburden, endotoxin
- Amounts of soils on surfaces
- Nature of soils on surfaces
  - Freshly deposited
  - Dried on during process
  - Dried on during dirty hold time
  - Baked on during process
  - Compacted



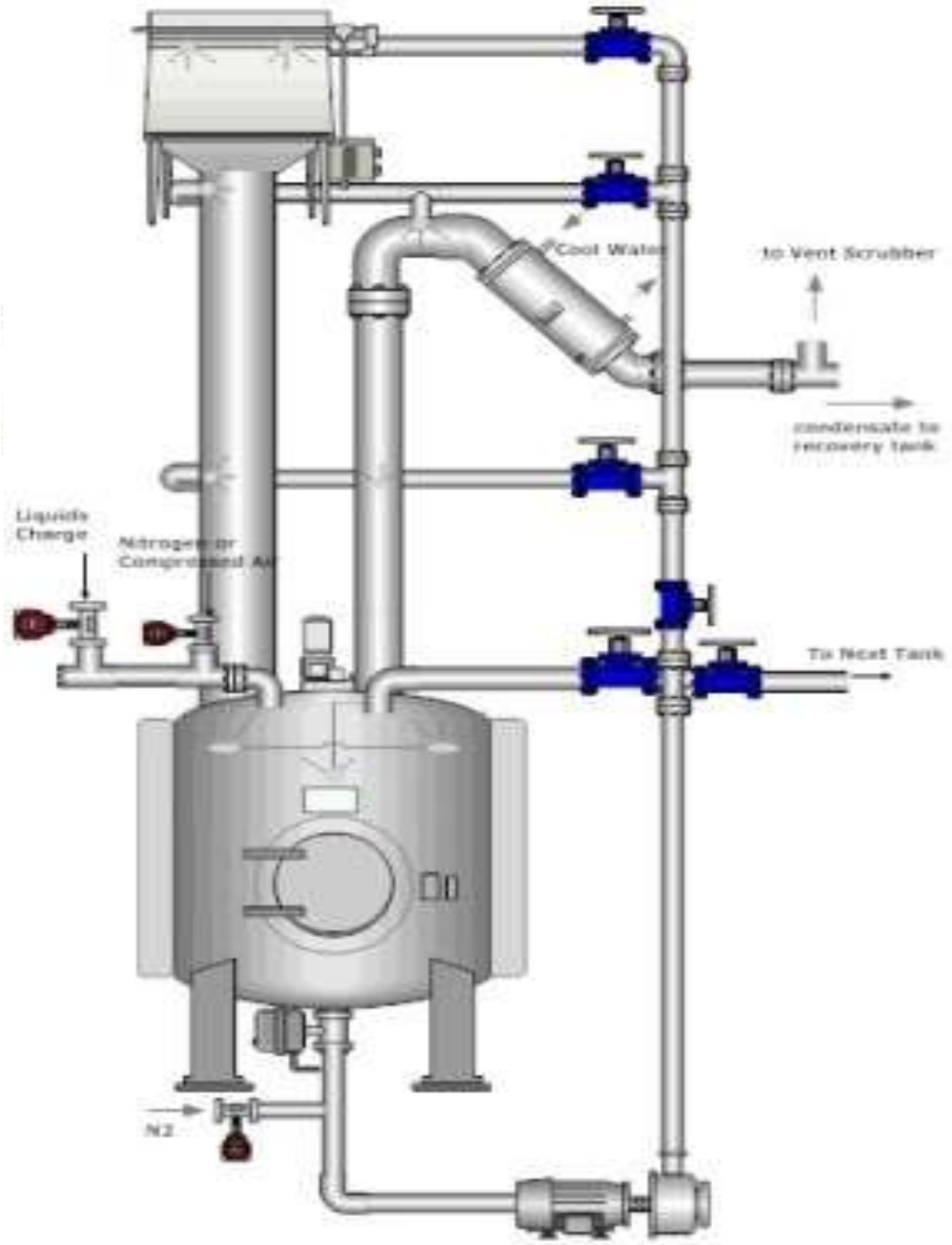
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Methods

- Extent of automation
- Extent of disassembly
- Examples
  - Fixed CIP
  - Portable CIP
  - Parts washer
  - Ultrasonic
  - Manual (soak, brush, wipe, spray)



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Methods Examples

Cleaning Agents Screening

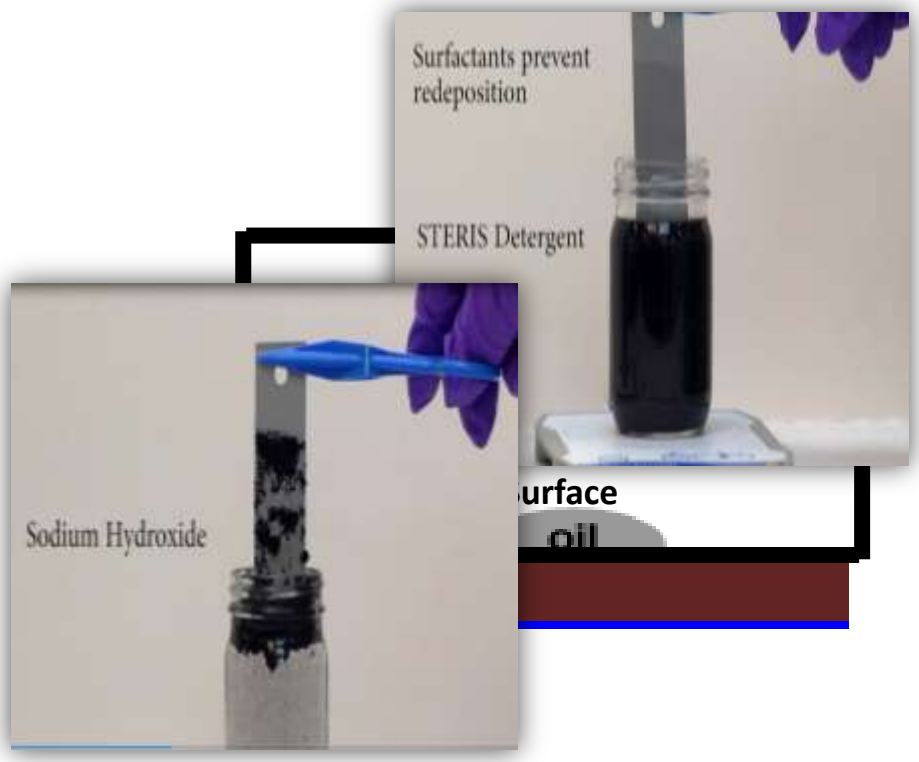
- Chemistry
- Performance
- Rinsability
- Substrate compatibility
- Supplier qualification
- Environmental health & safety
- Stability
- Toxicity
- Technical Support
- Global availability



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Cleaning components and mechanisms

- Solubility
- Wetting
- Emulsification
- Dispersion
- Hydrolysis
  - Chemical
  - Enzymatic
- Oxidation



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Residue limits

- What residues will I be testing for?
- How clean is clean?
- How low?
- Analytical methods used for measuring residues can perhaps affect selection of cleaning process, but is not typically a limiting factor



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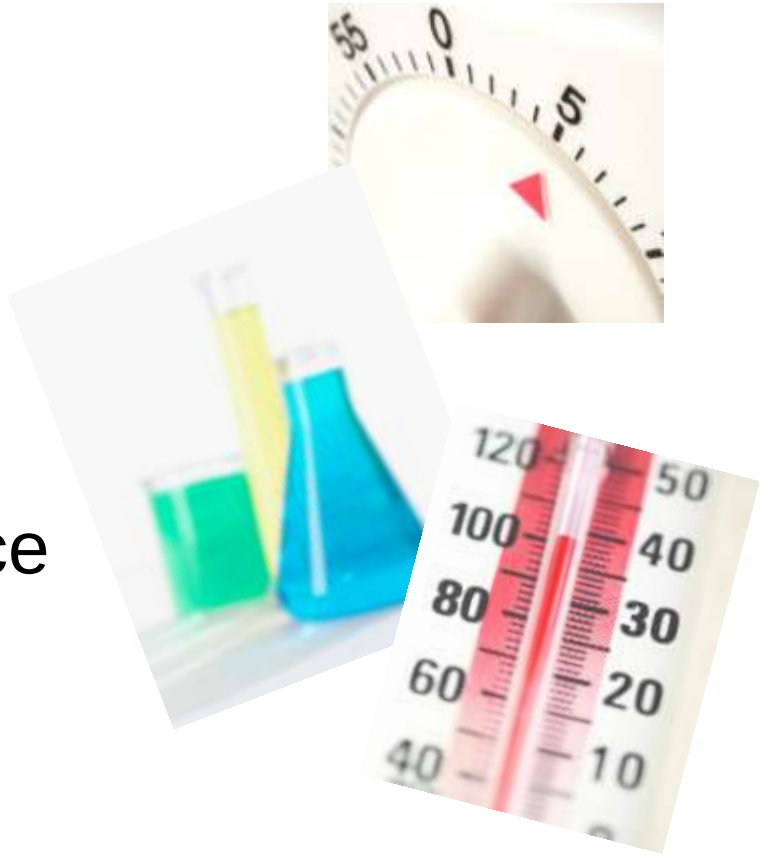
Defining critical parameters through experimental studies



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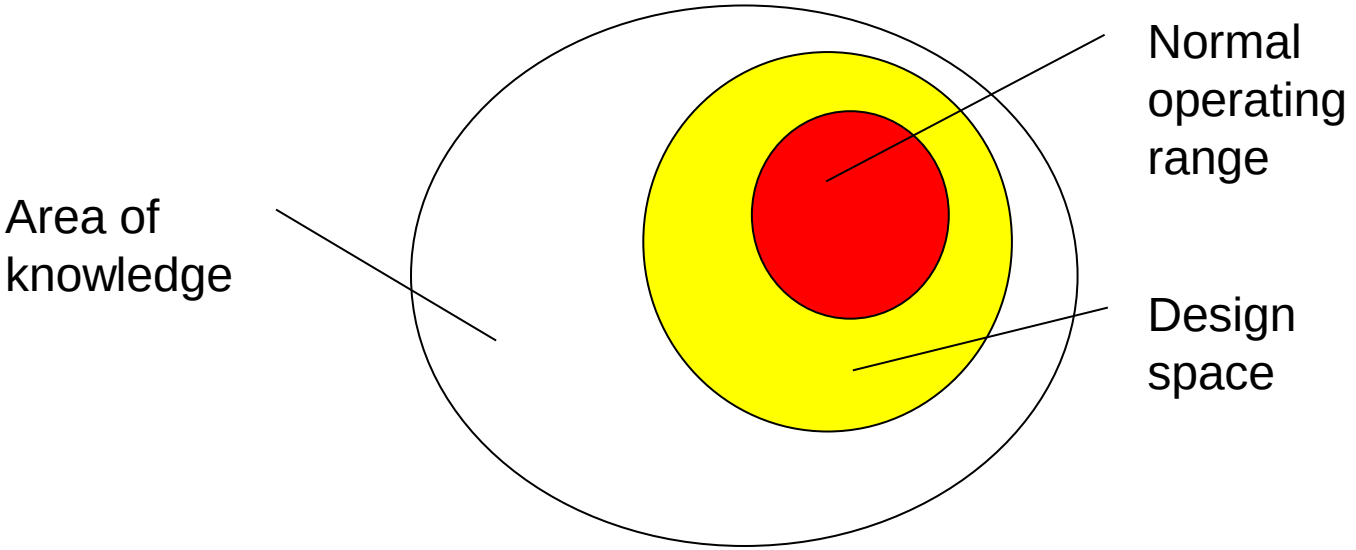
Critical cleaning parameters

- Time
- Action/impingement
- Cleaning chemistry
- Concentration
- Temperature
- Mixing/flow/turbulence
- Water quality
- Rinsing



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Critical parameters in a design space



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Dealing with variation

- Key concept in FDA Process Validation document is ID and control of sources of variation
- Design cleaning process to minimize variations
  - Control specification for times, temperatures, concentrations, etc.
- Design cleaning process with “worst-case” variables in mind



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Variation of CCP's

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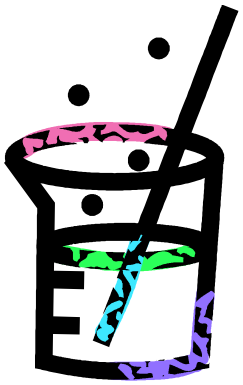
- Challenge at lower end (least stringent) of specification, or even below specification
- Example:
  - Temperature specification expected to be 70 ± 5°C
  - Perform lab/scale-up studies at set point of 65°C (lower end of specification)
  - Or perform lab/scale-up studies at set point of 60°C (below the lower end of specification), to determine robustness
- Stress in design phase so that challenge in validation protocol not needed



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Lab studies

- Lab studies done primarily to determine correct cleaning agent, cleaning agent concentration, temperature, and time
- Most companies that do lab studies do “beaker” studies



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Process And Cleaner Evaluation

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SS coupons are spiked with sample soil (s).



Soil conditions are emulated to the actual manufacturing process.



Coupons are exposed to multiple cleaning parameters depending upon customer's objectives.



Visually clean?

Water break free?

Weight change?



PACE form shipped with customer's samples.



PACE report summarizing the results and recommendations.

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Example of Lab Studies

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Cell Culture Bioreactor

- ***Air dried at ambient temperature for 2 hours***

Agitated Immersion:

CLEANER	CONC.	TIME/ TEMP	VISUAL OBSERVATION	"WATER BREAK-FREE"
Alkaline Detergent	**1 oz/gal**	**10 min / 40 °C**	**Visually clean**	**YES**
Alkaline Detergent	1 oz/gal	10 min / 80 °C	Visually clean	YES
Comparison Study: 1) NaOH followed by, 2) H_3PO_4	2.5 g/l 14.7 g/l	60 min / 80 °C	Slight residue	NO

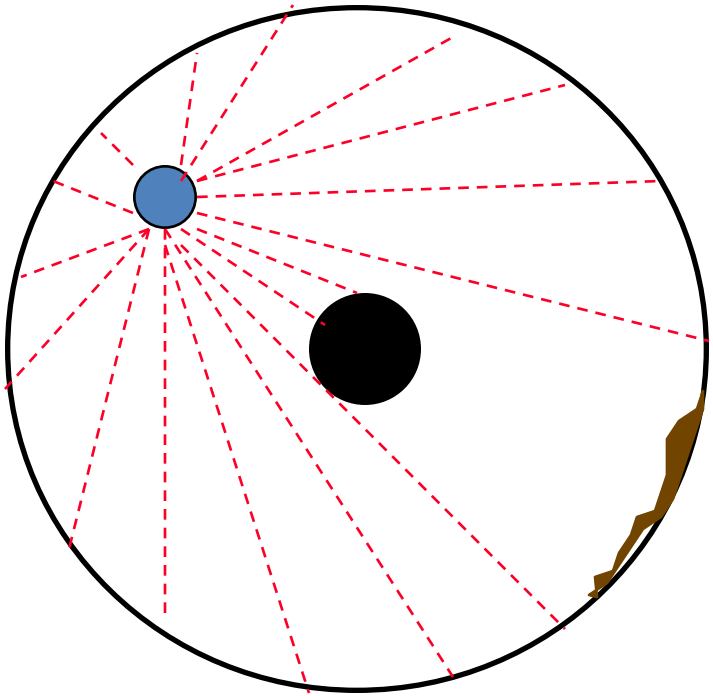
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Process equipment design review



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Cleaning solution coverage



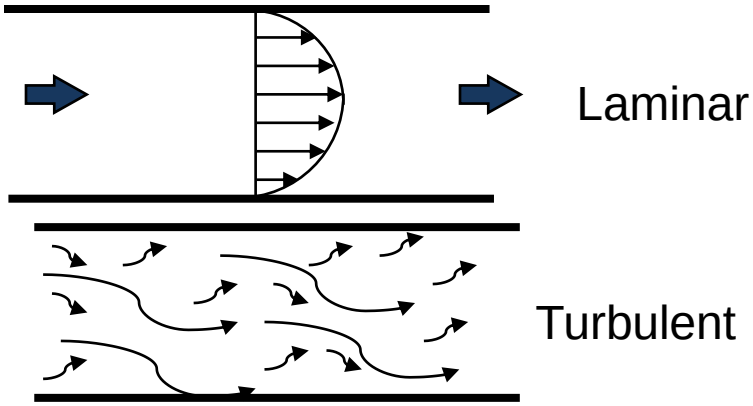
For vertical tanks:

Volumetric Flow rate (in GPM) of 2.5 to 3.0 times circumference in feet

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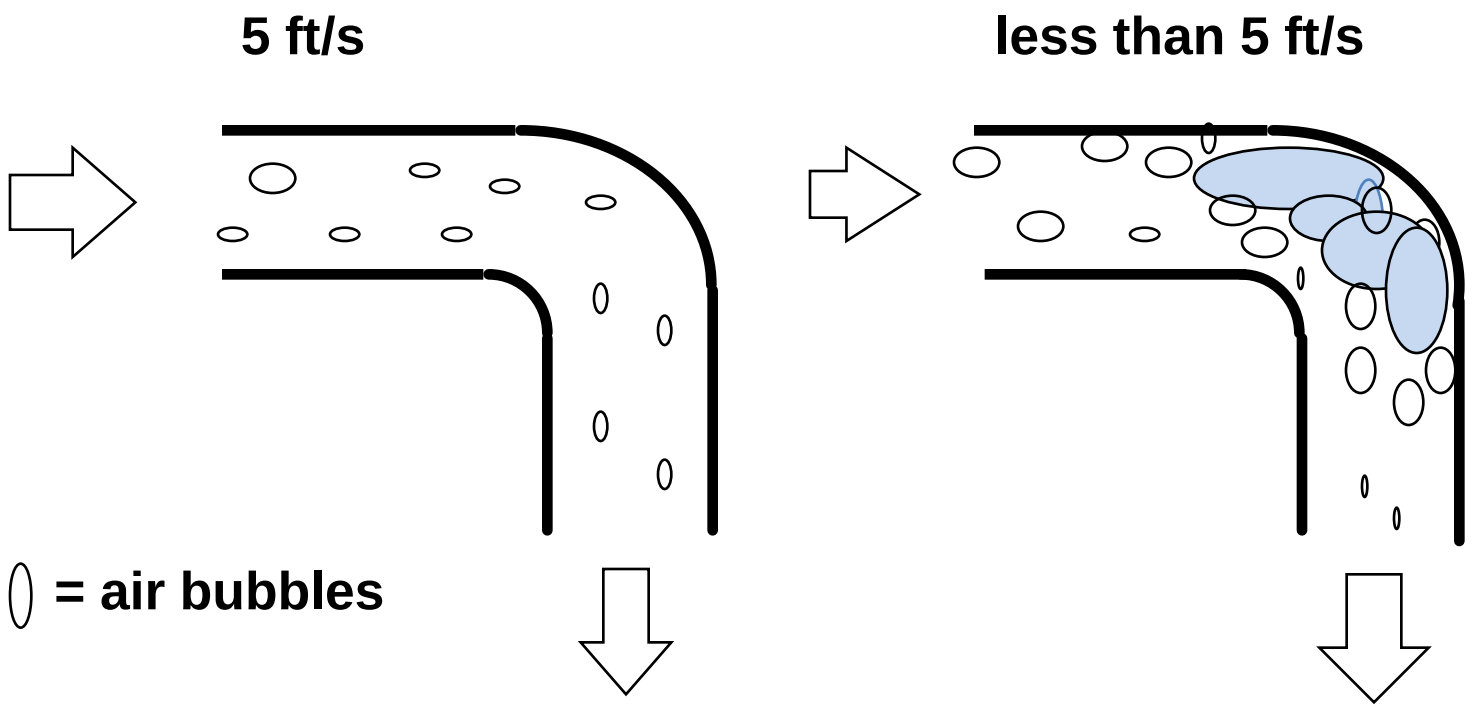
Cleaning pipes

- Reynolds Number (Re) larger than 4000 is described as turbulent flow.
- Re = 3162 Q / d k
  - Q=volumetric flow, (gal/min)
  - d= internal diameter (inches)
  - k= viscosity(cP) / specific gravity



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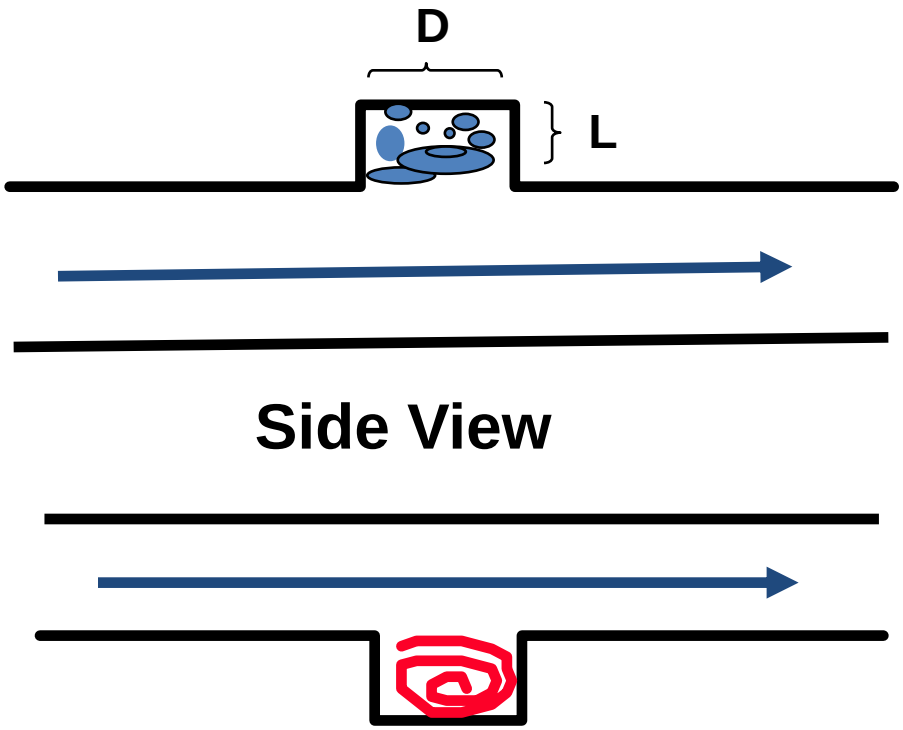
Fluid velocity

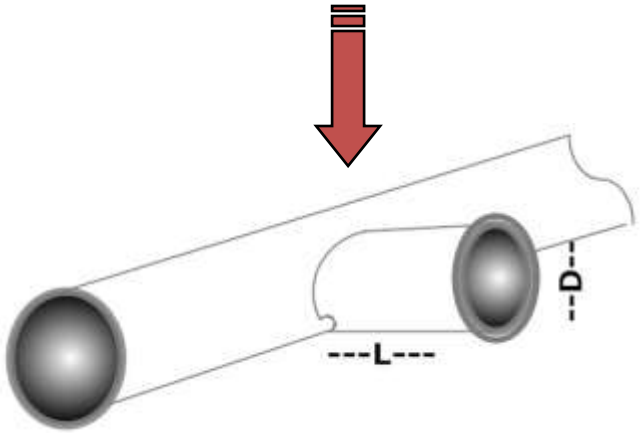


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Dead legs

L/D less than 1.5 is preferred



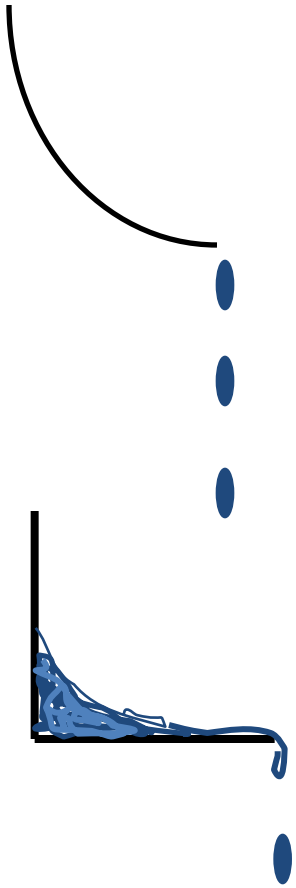


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Sanitary connections

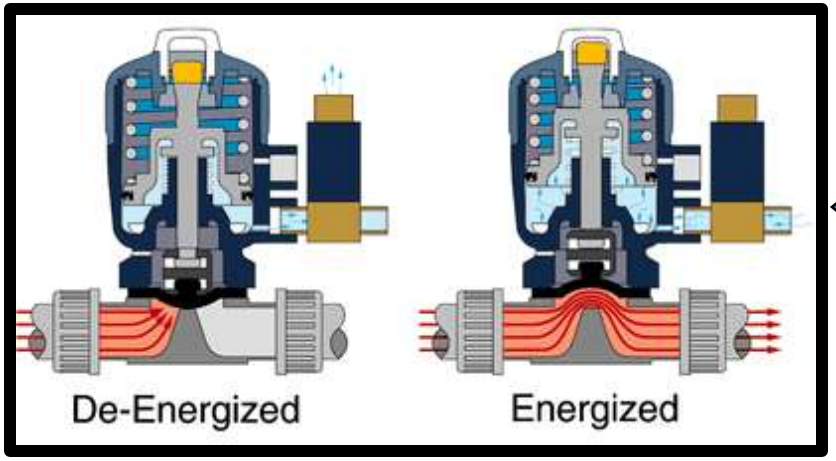
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- Welding is preferred for connecting pipes.
- Welded connection should not have excessive cracks, crevices, misalignments, or other surface deformities.
- “Sanitary” clamp-type connections for non-permanent connections.



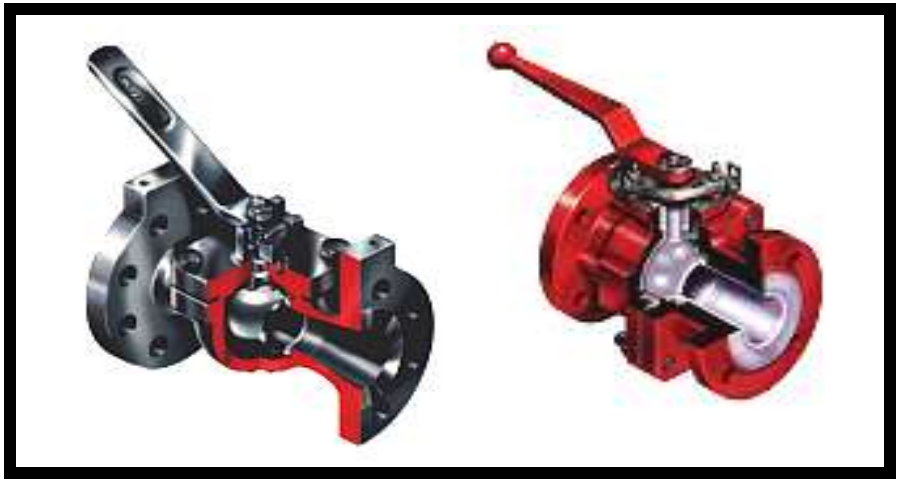
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Valves



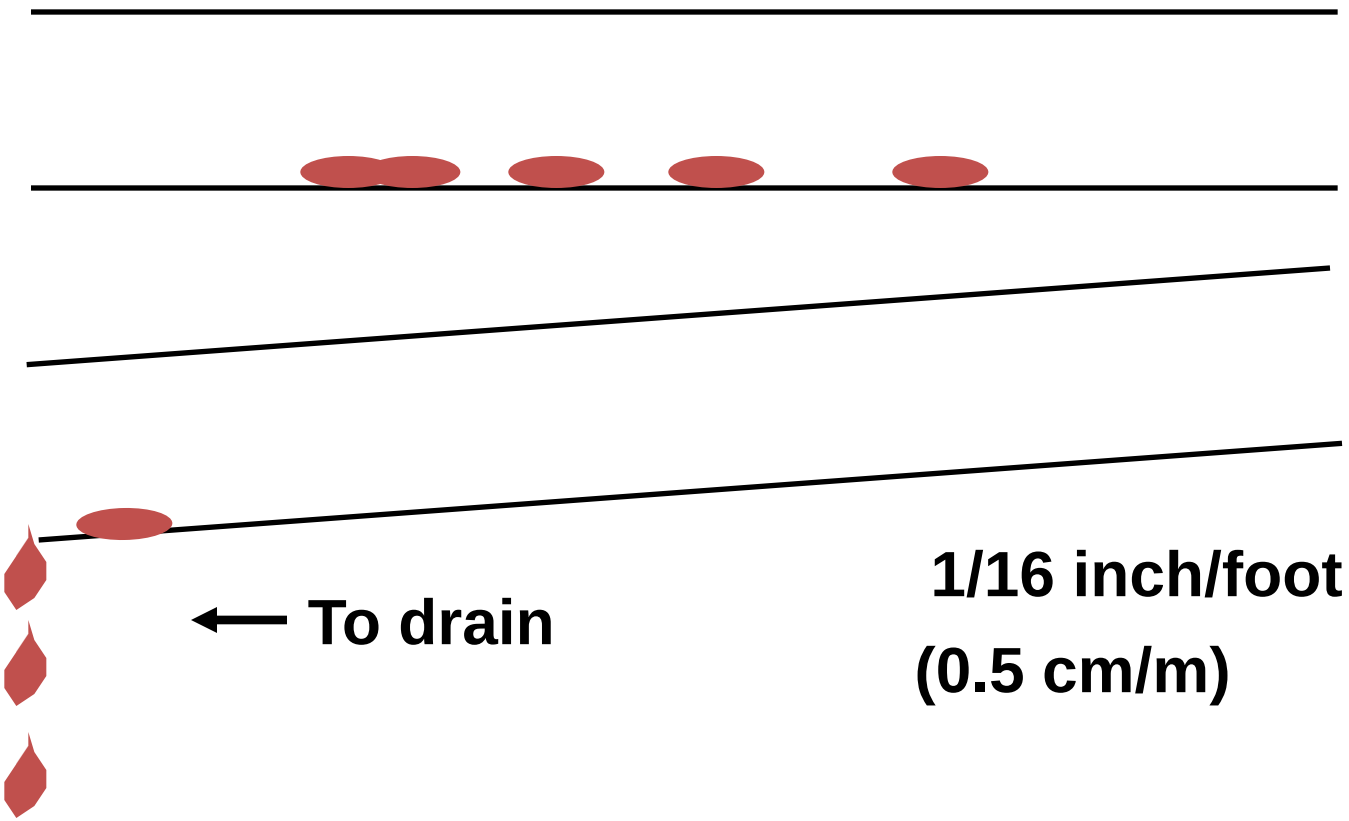
Preferred





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Drainability



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Materials of construction

- Surfaces should be non-reactive, non-porous, non-corrosive
  - Glass lined vessels
    - iso-corrosion curves for alkaline cleaners
  - Stainless steel
    - 304, 316, 316L
    - surface finish, rouge, passivation
  - Polymers
    - EPDM, silicon rubber, Teflon



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More information…

- Rivera. E. “Basic Equipment Design Concepts to Enable Cleaning in Place”. Pharmaceutical Technology.

  http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=726190
- Verghese G., P. Lopolito. *Cleaning Engineering and Equipment Design.* Cleaning and Cleaning Validation Volume I, ed. P. Pluta, published by DHI Publishing and the Parenteral Drug Association. Chapter 8. 2009, pp 123-150.



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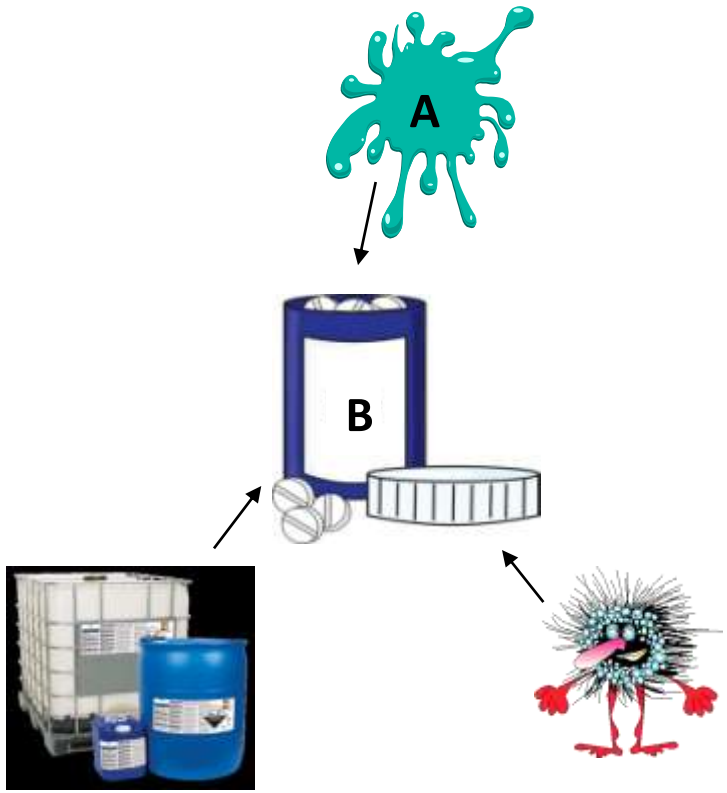
Scientific approach to establishing residue limits and acceptance criteria



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Possible target residues

- Drug active
- Cleaning agent
- Bioburden
- Endotoxin
- Degradation products or byproducts
  - API manufacture
  - Campaigns



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Acceptable level?

- Based on potential effects of target residue on subsequent product
- Possible effects & issues
  - Pharmacology of residue
  - Toxicity of residue
  - Dosing of next drug product
  - Stability issues
- May utilize a “safety” factor



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How low?

- Human Drug CGMP Notes, 9:2, 2Q 2001
  - "Should equipment be as clean as the best possible method of residue detection or quantification?"
  - Answer: "No,…absolute cleanliness is neither valuable nor feasible…. It should be as clean as can reasonably be achieved, to a residue limit that is medically safe and that causes no product quality concerns…."



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Acceptance criteria

Finished drug products

- Fourmen and Mullen approach for active
  - Most stringent of dose calculation and 10 ppm (in next product)

    AND
  - Visually clean
- PIC/S approach - most stringent of...
  - Dose calculation in next product
  - 10 ppm in next product
  - Visually clean



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Possible uses of “limit”

- Daily amount allowed per patient (µg or mg) – L0 (“L zero”)
- Concentration in next product (µg/g) – L1
- Absolute amount in manufacturing vessel train (mg) [MAC – maximum allowable carryover] – L2
- Amount per surface area (µg/cm^2) – L3
- Amount per swab (µg) – L4a
- Conc. in swab extract solution (µg/g) – L4b
- Conc. in “rinse” water (µg/g) –L4c



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Daily amount allowed – L0

- This has been called the Acceptable Daily Intake (ADI), Acceptable Daily Exposure (ADE),)Permitted Daily Exposure (PDE), Safe Daily Intake (SDI)
  - It is based on a safety/toxicity evaluation
- Values that have been used for L0
  - 0.001 of minimum daily dose of active
  - An ADI/ADE/PDE value based on toxicity information



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L0 selection?

- Which L0 value to use?
- Traditionally, dose-based calculation for actives
  - Exception has been where active is allergenic, mutagenic, cytotoxic, etc. (highly hazardous actives)
- Traditionally, toxicity calculation for cleaning agents or other materials without a dose



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L0 selection? (2)

- Can ADE values (from Risk-MaPP) or PDE values (From EMA) be used for non-highly hazardous actives?
  - Yes. Will generally result in higher limits as compared to 0.001 dose.
- Sometimes if can't measure limit based on 0.001 dose, will evaluate ADE?PDE to set a higher limit so it is analyzable



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In subsequent product – L1

- Safe concentration in next product:

$$\frac{L0}{\text{Max. daily dose of next drug product}}$$

or

10 ppm in subsequent product

WHICHEVER IS LOWER!

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Absolute amount limit – L2

- Absolute amount in manufacturing vessels [MAC]
- Calculate by multiplying L1 limit times batch size of subsequent product
  - Use *minimum* batch size if next product made in multiple batch sizes



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Limit per surface area – L3

- Calculated by dividing L2 by shared surface area (of equipment train – evaluate *cumulative* effect)
- Example:
  - L2 = 2,000,000 µg
  - Shared surface area is 450,000 cm^2
  - L3 (limit per surface area) is
    2,000,000 µg / 450,000 cm^2 = 4.4µg/cm^2
- Assumes uniform distribution (worst case for setting limit)



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Limit per swab – L4a

- Amount per swab depends on
  - Limit per surface area (L3)
  - Swabbed area
- Calculate as
  - L4a = L3 X swabbed area
- Example: swab area is 25 cm^2 and L3 is 4.4 $\mu g/cm^2$ then
  - L4a = 4.4 $\mu g/cm^2$ X 25 cm^2
  - L4a = 110 µg (of active of A)



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Limit in swab extract – L4b

- Concentration in swab extract depends on
  - Limit per surface area (L3)
  - Swabbed area
  - Amount solvent for extraction
- Calculate as

$$\frac{\text{L3 X swabbed area}}{\text{solvent extraction amount}}$$

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Leveraging sampling

- L4b change based on *volume* for extraction
  - If extracted into 20 g solvent,
    110 μg / 20 g = 5.5 μg/g
  - If extracted into 10 g solvent,
    110 μg / 10 g = 11 μg/g
  - If extracted into 5 g solvent,
    110 μg / 5 g = 22 μg/g



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Leveraging sampling (2)

- L4b change based on *swabbed area*
  - If swab 25 cm^2 and extracted into 20 g solvent,
    110 μg / 20 g = 5.5 μg/g
  - If swab 100 cm^2 and extracted into 20 g solvent,
    440 μg / 20 g = 22 μg/g
  - If swab 100 cm^2 and extracted into 5 g solvent,
    440 μg / 5 g = 88 μg/g



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Overall equation for L4b

$$\frac{(0.001)(\text{min.dose Act.A})\ (\text{B.S.})\ (\text{S.A.})}{(\text{max.dose Prod.B})\ (\text{S.S.A.})\ (\text{S.E.A.})}$$



For swab sample, where:

B.S. = minimum batch size Prod.B

S.A. = sampled area

S.S.A. = shared surface area

S.E.A. = solvent extraction amount

Use care in units! (µg/g or µg/mL = ppm)

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Recovery?

- May include recovery in limit calculation
  - Multiply L4 by recovery (expressed as decimal)
  - Compare measured value to that limit
- Better is to keep L4 “pure”
  - Divide measured value by recovery (expressed as decimal)
  - Compare “corrected” measured values to L4



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“Rinse” solution limits – L4c

- Meaning of “rinse” solution limits?
  - How relate to concentration in next product (L1)?
  - Is 5 ppm in “rinse” solution (L4c) same as 5 ppm in next product (L1)?



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Rinse calculations

- Calculation of L0, L1, L2, & L3 are exactly the same
- Only difference is L4c
- Overall equation:

$$\frac{(0.001)(\text{min.dose Act.A})\ (\text{B.S.})\ (\text{S.A.})}{(\text{max.dose Prod.B})\ (\text{S.S.A.})\ (\text{S.E.A.})}$$

- Sampled area and solvent extraction amount need to be defined



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“Non-dose” modifiers

- Effects of actives other than therapeutic effects
  - Mutagenicity
  - Cytotoxicity
  - Allergenicity
  - Reproductive hazards
- Traditional approach
  - Require dedicated equipment
  - Not detectable by best available technique



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“Non-dose” modifiers (2)

- Newer approaches
- Determine safe daily amount for lifetime exposure based on safety evaluation
  - Risk-MaPP approach for ADE (Acceptable Daily Exposure)
  - EMA proposed approach for PDE (Permitted Daily Exposure)
- May include deactivation step



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L0 for HHAs – ADE Approach

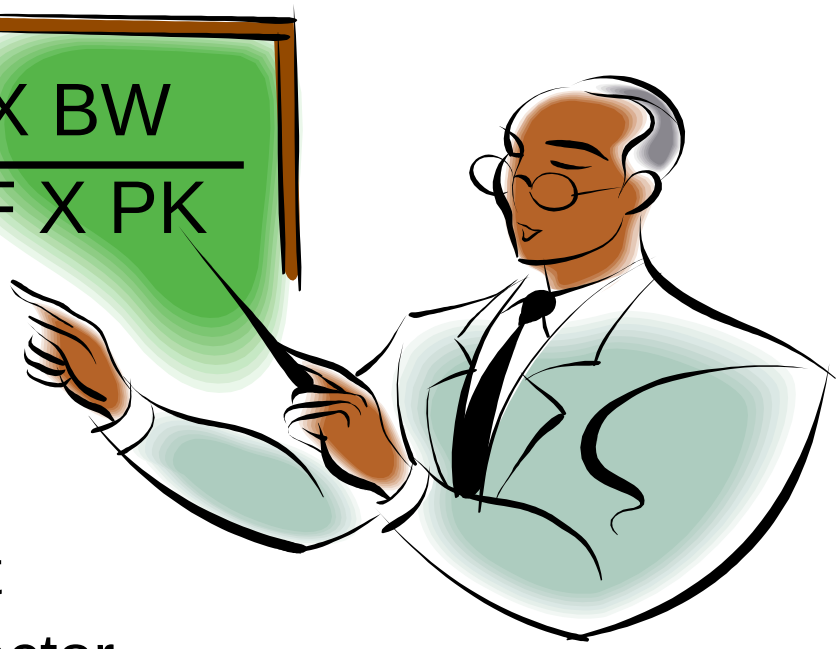
- Based on an animal study, a NOAEL (No observed *Adverse* Effect Level) is determined based on that critical effect
  - Example: If critical effect is reproductive toxicity, then highest level with no observed toxic effect is NOAEL
- A NOAEL is not a safe level
  - Limited data points
  - Transfer from animal model
- Further adjustment factors applied by toxicologist



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Complete equation

$$ADE = \frac{NOAEL \times BW}{UF_C \times MF \times PK}$$



Where:

BW is body weight

MF = Modifying Factor

UF_C = Composite Uncertainty Factor

PK = Pharmacokinetic Adjustment(s)

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Cleaning agent limits

- Use same principles as for finished drugs for limit in subsequent product
- Main difference is no dose
- For L0, use ADI based on toxicity information
- ADI estimated based on LD_{50}
  - Same route of administration

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ADI calculations

$$ADI = \frac{LD_{50} \text{ X body weight}}{\text{(conversion factor)}}$$

$$L1\ (ppm) = \frac{\text{ADI of cleaning agent X } 10^6}{\text{maximum dose of next product}}$$

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Example

- Cleaner with oral LD_{50} of 860 mg/kg
- Subsequent product dosed at max. of 15 grams (or 15,000 mg) per day for 60 kg person
- Conversion factor of 100,000 for ADI purposes (for example)



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Conversion factor references

D L Conine, B D Naumann, and L H Hecker, Setting Health-Based Residue Limits for Contaminants in Pharmaceuticals and Medical Devices, *Quality Assurance: Good Practice, Regulation, and Law*, Vol. 1, No. 3, pp. 171-180 (1992).

H J Kramer, W A van den Ham, W Slob, and M N Pieters, Conversion Factors Estimating Indicative Chronic No-Observed-Adverse-Effect Levels from Short-Term Toxicity Data, *Regulatory Toxicology and Pharmacology*, vol. 23, pp 249-255 (1996).

D.B. Layton, B J Mallon, D H Rosenblatt and M J Small, Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data, *Regulatory Toxicology and Pharmacology*, Vol. 7, pp. 96-112 (1987).



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Example (cont.)

- ADI = $\frac{860 \text{ X } 60}{100{,}000}$ = 0.52 mg

- L1 = $\frac{0.52 \text{ X } 10^6}{15{,}000}$ = 35 ppm

(Use this to calculate L2, L3 and L4; will usually result in surface area limit well above visual limit)

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Grouping strategies for products and equipment



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Grouping strategies

- Grouping
  - By product (soil)
  - By equipment
- Reason for grouping
  - Simplify amount of validation work
  - Less analytical method validation and recovery studies
  - Fewer validation runs



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Terminology

- Grouping approach
- Matrix approach
- Family approach
- Bracketing



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Forming a product group

- Conditions to meet for product grouping
  - Similar product type
  - In same equipment train
  - Same cleaning process
- Products can have different actives!



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Representative product

- Representative: most difficult to clean
- Basis of selection
  - Historical (usually anecdotal)
  - Solubility data
    - Based on active?
    - Solubility at what pH?
  - “Point” system
  - Lab/pilot study



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Residue limit selection

- Lowest limit among group:

Product	Active	Limit (L3)
A	M	25 µg/cm^2
B	N	15 µg/cm^2
C	O	30 µg/cm^2
D	P	10 µg/cm^2

- If product A is worst case (most difficult to clean), then validate Product A at limit of 10 µg/cm^2 of M.



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Equipment grouping

- Select equipment that is in group
- Select representative equipment
  - Worst case for cleanability *if a worst case exists*
- Decide extent of validation runs



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Equipment in group

- For cleaning, must be same type
  - Cannot group ribbon blender and V-blender
- Normally involves *identical* equipment
  - Identical by IQ/OQ
  - Limit to “identical for cleaning purposes”
    - Some differences may not relevant to the cleaning situation



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Other Differences

- Select worst case or bracket for:
  - Size difference
  - Complexity difference



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Documentation of process design phase



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Value of lab studies

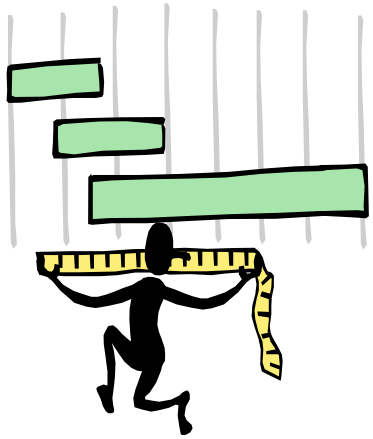
- Selection of initial specifications
  - Cleaning agent?
  - Concentration?
  - Temperature?
  - Time?
- For stressing parameters
- For worst-case product in grouping approach



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Scale-up

- Next step is confirmation (or modification) in pilot scale/plant evaluation
  - Confirm lab performance
  - Confirm key control parameters
  - Confirm adequate engineering (address flow paths, dead legs, etc.)
  - Optimize time(s), conditions
  - Determine rinse conditions
  - Identify potential sampling locations
  - Evaluate with analytical method



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Full scale runs

- Based upon lab and scale-up studies, as well as data on related cleaning processes, may either:
  - 1. Perform confirmatory study or studies at full scale (prior to validation runs)
  - 2. Go immediately to validation protocol run(s)



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Documentation



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Other miscellaneous issues to consider during this stage

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Water quality

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Effects on...

- Washing
- Rinsing

	Endotoxin	Organics	Salts	Ca/Mg salts	Bacteria
WFI	X	X	X	X	XXX
PW		X	X	X	XX
De-ionized			X	X	X
Softened				X	X
Tap					X

"X" means issue is addressed in water quality



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Compressed gases

- Compressed air or gas may be used to:
  - blow down of wash or rinse fluids
  - drying step
- Risks may include contamination with condensate, oil, and viable/non-viable foreign particulates.
- Gas blow down before the post-wash rinses to remove residual cleaning agent and process soil should be:
  - short
  - ambient temperature



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Room environment

- The environment or building management system controls humidity, room temperature and particulate levels all of which may contribute to effective or in-effective cleaning procedures.
- Humidity and room temperature should be defined and monitored.

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Stage 2: Process Qualification

Science & Solutions for Life

Analytical method validation



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Target chemical residues

- Method dependent upon type of residue
- Select target residues first
  - Active
  - Excipient (?)
  - Cleaning agent
  - Cleaning agent component



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Specific methods

- Can give exact amount present of targeted species in presence of expected interferences
  - High Performance Liquid Chromatography (HPLC, or UHPLC)
  - Ultraviolet Spectroscopy (UV)
  - Ion Chromatography (IC)

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Non-specific methods

- Cannot give exact amount present, but can give assurance that are at or below the measured amount
  - TOC
  - Conductivity
  - Titrations



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Non-specific strategy

- Measure non-specific property, and calculate residue *as if* all of measured property is due to that residue
- Provides upper limit value
- Example
  - TOC of swab sample = 1.2 ppm
  - %C of active = 30%
  - Maximum active in sample = 4.0 ppm
  - Compare to acceptance limit



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Drug product residues

- Drug active
  - Other things being equal manufacturers should prefer specific assay – WHY?
  - If degraded during cleaning, measure gross property (TOC) or, if justified, measure degradant
  - May degrade by heat, pH, oxidant
- Generally don't target excipients

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Cleaning agents

- Generally expected to measure cleaning agent
- Two analytical approaches
  - Measure individual species (representative) within cleaner
  - Measure gross property (e.g., TOC)



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ICH Q2(R1)

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	ID	Impurity Quant.	Impurity Limit	Assay
Accuracy	-	+	-	+
Repeatability	-	+	-	+
Intermediate Precision	-	+	-	+
Specificity	+	+	+	+
DL	-	-	+	-
QL	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+



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Method validation

"Analytical methods should be validated before the cleaning validation study is carried out". **PIC/S PI 006-3**.

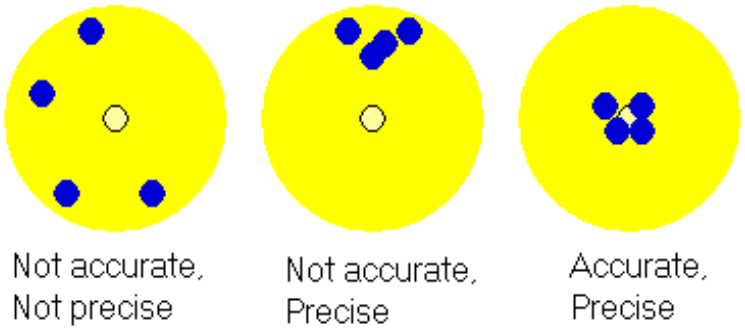
- Assurance that key part of validation accurately performs
- Focus on values in analytical sample (L4), NOT in next product (L1)



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Method validation

- Accuracy - closeness to true value
- Precision - closeness among measurements
- Range
- Linearity
- LOD/LOQ



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Appropriate range?

- Residue limit is upper value
- Desire linear range around expected values in analytical sample
- Why validate at 50-200% of limit?
- Ranges (in analytical sample) of interest --
  - 20-100% of limit
  - 50-150% of expected value
  - 1X-8X of LOQ



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Intermediate precision

- Different days
- Different analysts
- Different instruments
- Different reagent lots
- Independently prepared standards

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Purpose of sampling

- Adequately quantify residues on defined surfaces
- Usually involves removing residues from surfaces



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Sampling methods

- Swab (“Direct”)
- Rinse (“Indirect”)



Courtesy of Texwipe



Coustesy of EP Scientific Products

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Swabs

- Advantages
  - Can focus on worst case locations
  - Mechanical means of removing substances
- Issues
  - Swab must release analyte
  - Care in swab handling procedures
  - Interferences from swab
  - Swabbing is a manual procedure
  - Access to sampling sites



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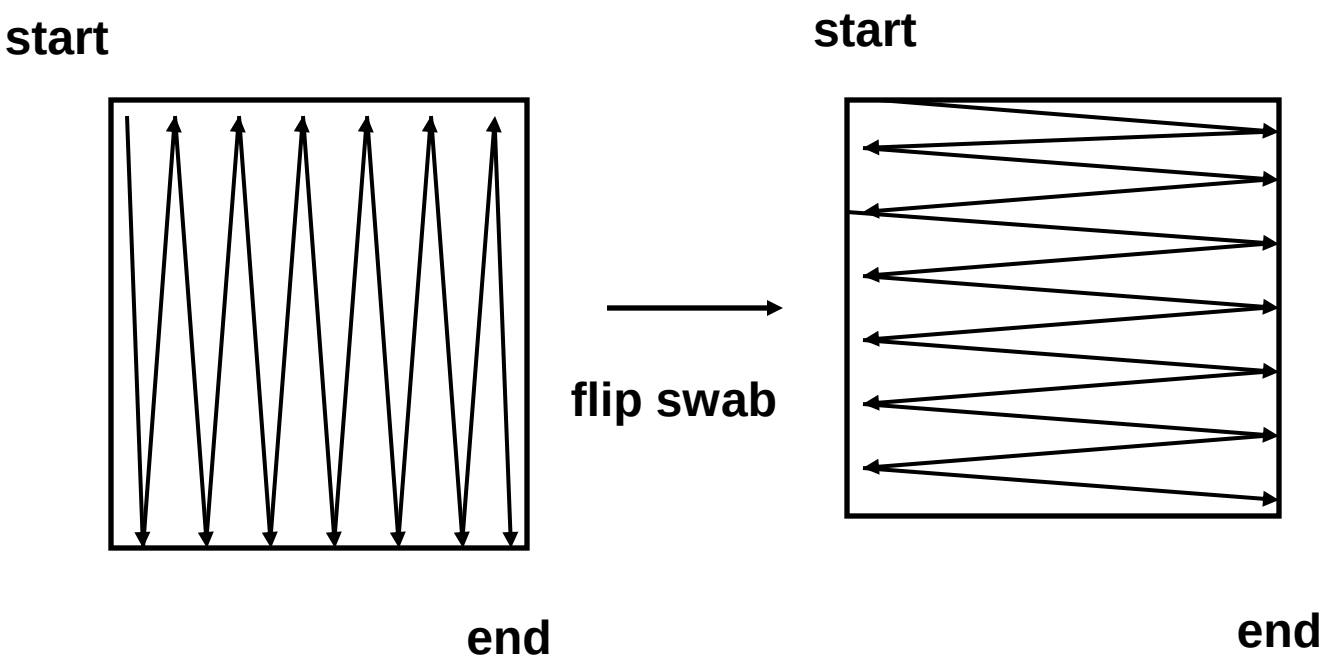
Swabbing SOP

- Specify swab (supplier and part no.)
- Specify surface area to be swabbed (usually 25-100 cm^2)
- Specify wet or dry (& solution, if wet)
- Specify template (if used)
- Specify number of swabs per site
- Specify swabbing pattern



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Swab pattern example



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Swab sampling locations

- Most difficult-to-clean locations
  - Engineering judgment, common sense
  - Prior experience
  - Sub-optimal cleaning process
- Sites for non-uniform contamination of next product
- Different materials
  - Glass, steel, gaskets
- Functional locations
  - Blades, tank walls, fittings



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Rinse sampling

- Definition: Using a solvent to contact all surfaces of sampled item to quantitatively remove target residue
- Solvent can be water, water with pH adjusted, or organic solvent
- Must contact all surfaces
- Residue measured in collected sample



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Rinse sampling (2)

- Advantages
  - Sample “inaccessible” locations
  - Provides overall picture (averages)
- Issues
  - Solubility of residue in rinse solution
  - Need to relate amount in rinse sample to potential contamination of next product (set limits appropriately)



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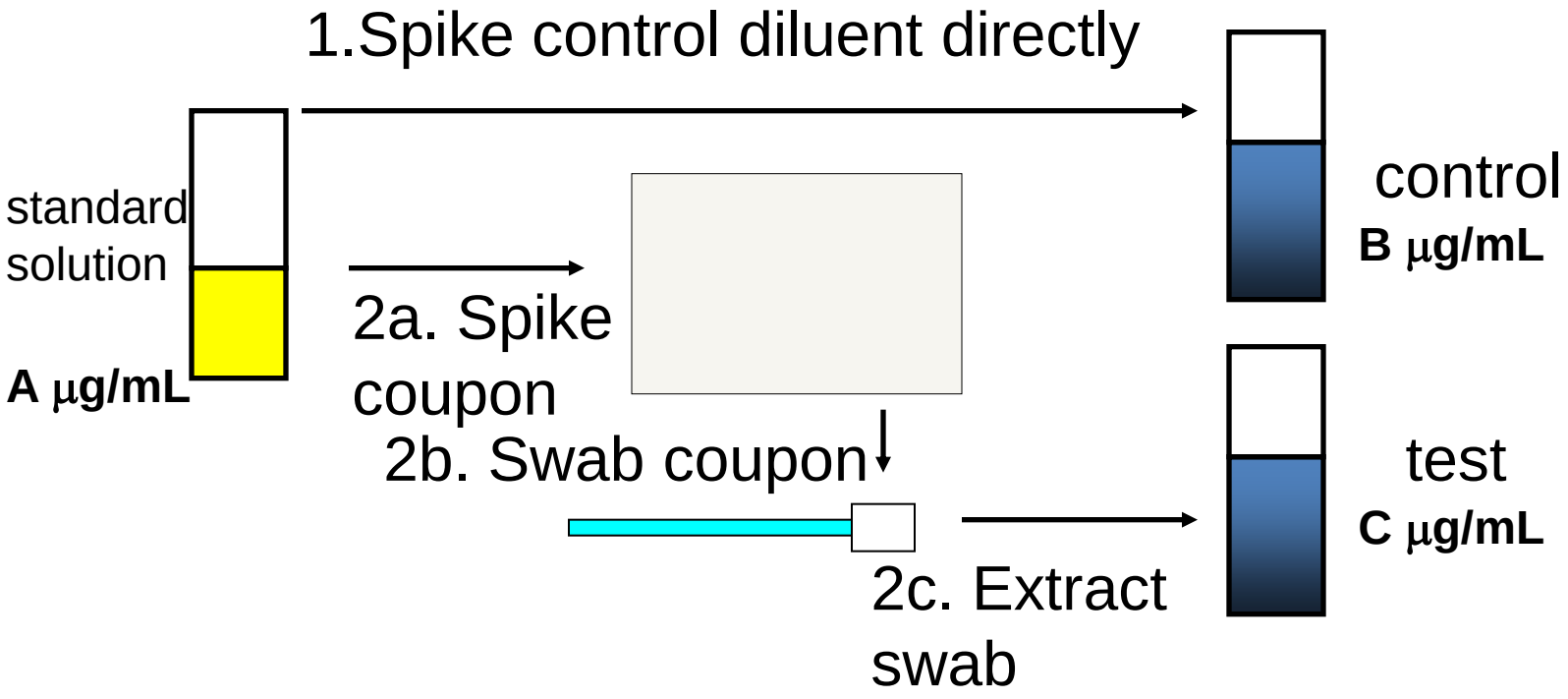
Recovery studies

- Recovery study - swabs & rinse
- Procedure
  - Spike coupon with known amount
  - Allow to dry
  - Remove in swab or simulated rinse procedure
  - For swab, desorb
  - Analyze sample
  - Compare to expected 100% value
- Done at (or below) surface acceptance limit



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Recovery schematic



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Different analysts

- Use lowest average of any sampler
  - Usually 3 replicates by one sampler
  - Some use lowest value of any one run
- Spiked at 2 $\mu g/cm^2$
- Three samplers
  - 1: 85% recovery
  - 2: 82% recovery
  - 3: 73% recovery
- Utilize 73% for analytical corrections



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Different surfaces

- As a general rule, are expected to *address* all product contact surfaces types in equipment
- Examples of types: SS, glass, PE, PP, nylon, silicone, EPDM
- If have one type with different surface finishes (e.g., different finishes of 316L stainless), perform recovery on “roughest” and apply to all finishes for stainless
- May also consider 316L, 316, and 304 stainless the “same”



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Different surfaces (2)

- Option 1: Recovery for every surface type
- Option 2: Recovery for any surface type above X% of total surface area
  - If X% or less, use a minimum as a default (e.g., 50%)
  - If X% or less, use the lowest any similar surface type (metallic, hard plastic, soft plastic)



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Different surfaces (3)

- Option 3 – Grouping of surface types
  - Recovery on representative MOC based on data analysis or designed studies
  - Conclusion may be that recovery on a certain surface provides support for same recovery on other surfaces

Merck: http://pharmtech.findpharma.com/pharmtech/Article/Materials-of-Construction-Based-on-Recovery-Data f/ArticleStandard/Article/detail/463714

Eli Lilly: http://pharmtech.findpharma.com/pharmtech/Peer-Reviewed/A-Risk-Management-Approach-to-Cleaning-Assay-Valid/ArticleStandard/Article/detail/673452



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Acceptable recovery

- Specify in cleaning validation master plan
- To correct data, usually specify a minimum of 50%
  - May allow <50% with written justification

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Rinse recovery

- More difficult to duplicate in lab
- Approximate rinse conditions
  - Solvent quality
  - Temperature
  - Flow/agitation
  - Ratio of volume to surface area
  - Time
- If approximate, be conservative
  - Example, lower volume to area ratio

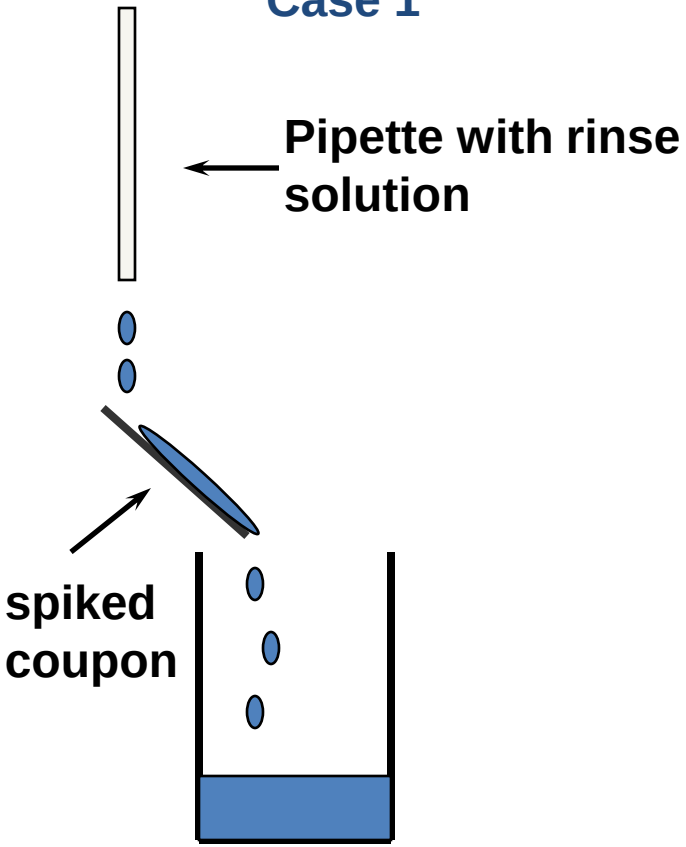


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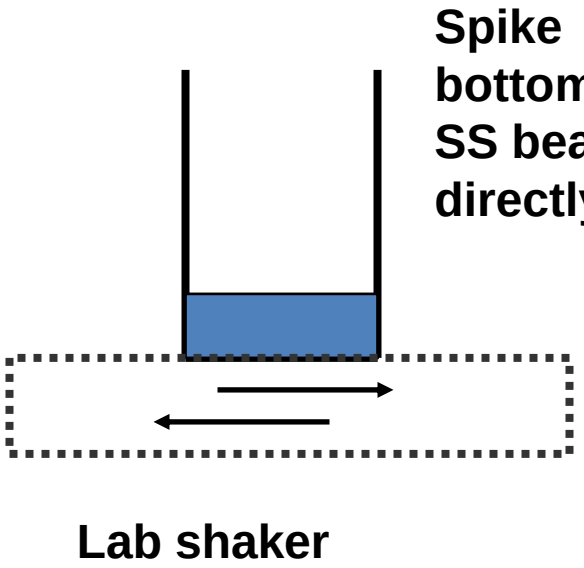
Lab simulations

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Case 1



Case 2



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Rinse recovery issues

- Not operator dependent – one study adequate
- For Case 2, if beaker of suitable material is not available, consider adding a spiked coupon to an glass or stainless beaker
- If coupon floats, place spiked side down



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Microbial methods and sampling



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Bioburden limits

- Good cleaning factors hostile to microbes
  - High temperature
  - pH extreme
  - Oxidizer (biocidal)
  - Surfactant (wetting, physical removal)
- Removal of chemical residues --
  - Microbe “trap”
  - Nutrient
- In most cases, effective cleaning can result in good control (<25 or 50 CFU/25 cm^2)

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Limit for microbes

- For chemical residues, can predict level in next product and estimate effects
- Microbes are living organisms –
  - Must consider proliferation in next product
- Consider
  - Species (objectionable organisms)
  - Further processing of subsequent product
  - Preservative in subsequent product
  - Level based on past practices, baseline data, and/or industry standards
  - May also affect endotoxin levels



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Bioburden rinse limit

- Calculated limits extremely high
- For PW rinse, consider default as PW limit (100 CFU/mL)
- For WFI rinse, consider value intermediate between PW and WFI limits (1-10 CFU/mL)
- Consider need to subtract blank



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What if SIP?

- Still want to control and measure bioburden
  - Consistency in SIP process
  - Endotoxin control
- Even more concern in biotech with good bioburden control



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Endotoxin limits

- Generally only set limits for finished drug manufacture for parenteral and inhalation products
- Limits are set at “industry standard” of WFI specs in rinse water (0.25 E.U./mL)
- Difficult to measure on surfaces



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Micro sampling

- Conventional micro tools
  - Rinse water, with membrane filtration or pour plate count
  - Swab, with desorption and plate count
  - Contact plate
- Focus is aerobic bacteria, but may have to consider molds/yeasts
- No additional method validation needed for approved micro lab procedures
- No recovery from surfaces required



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Cleaning documentation readiness

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Validation protocols

- Scope/Objectives
- Responsibilities
- Equipment
- Cleaning methods
- Sampling
- Analytical procedures
- Acceptance criteria
- Documentation
- Equipment/sample diagrams
- Monitoring worksheets



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Detail vs. by reference

- Need key info as detail or by reference
  - How limits calculated
  - How sampling location selected
  - Worst case process conditions
- Protocol for people executing it; keep it streamlined
- But: Adequate short descriptions for reviewers to know how was done



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Worst-case conditions

- FDA process validation guidance (1987):

  “The test conditions for these runs should encompass … those within standard operating procedures, which pose the greatest chance of process or product failure compared to ideal conditions; such conditions have become widely known as "worst case" conditions.”



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2011 PV guidance

- No mention of “worst case” conditions
- “The PPQ lots should be manufactured under normal conditions by the personnel routinely expected to perform each step of each unit operation in a process.”
  - Removed statement that was in draft guidance about conditions that pose a high risk of process failure.



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PQ conditions

- Traditional approach
  - Worst cases for PQ runs
  - Challenges for PQ runs
  - Process conditions (within normal process ranges)
  - Minimum of 3 runs to show consistency



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PPQ conditions

- Possible new approach (new PV approach from FDA)
  - Identify sources of variation
  - Design cleaning process to
    - Reduce sources of variation
    - Minimize the effects of those variations
  - Best done in design and development, not in PPQ runs



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Equipment qualification and utilities readiness

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Utility readiness (1)

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- All direct impact utilities for cleaning must be properly qualified.
  - Generation and distribution systems of a utility must be approved prior to use for a cleaning procedure.
  - Non-product contact utilities must have an installation review as per Good Engineering Practices.



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Utility readiness (2)

- USP grade water generation systems must be qualified.
  - Final rinse water must be of the same quality or better as that used for the manufacturing process.
- Solvents used for rinsing must be of a defined grade and from a manufacturer which is approved by the user.



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Equipment readiness

- IQ and OQ protocols for new, existing, or modified manufacturing equipment must be completed.
- All spray devices used for cleaning solution distribution (e.g CIP systems) should be qualified for ensuring proper coverage.
- Computerized systems required for the operation and monitoring of the cleaning process must be done before initiating a cleaning validation run.



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Spray device qualification
(coverage test)

- Procedure
  - Coat with riboflavin (0.2g/L)
  - Observe with UV light while wet
  - Dry and then short rinse cycle with water
  - Observe with UV light while wet
- If poor coverage, make changes and repeat until 100% coverage

No Contact…. No Cleaning!

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Personnel training program and tools



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Personnel training (1)

- Plant personnel that participate in the execution of cleaning validation protocols and procedures must be trained prior to performing any the activities (ref. 21CFR210-211).
- Levels of training may vary from a general awareness to live demonstrations.

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Personnel training (2)

- The following areas are typically involved in cleaning validation activities:
  - Validation
  - Quality Assurance
  - Operations
  - Facilities
  - Quality Control Laboratory
  - Engineering



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Example of training tools

Visual inspections:

- Camera
- Flash light
- Magnifier
- Inspection mirror
- Boroscope



Sampling:

- Sampling locations for rinse and swabbing
- Swabbing kit
- Contact plates

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Validation execution



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Cleaning runs (1)

- The cleaning validation run must be performed at the end of manufacturing campaigns.
- The campaign length is determined by production planning.



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Cleaning runs (2)

- Cleaning process can be considered validated for the longest campaign (highest number of lots) that preceded one of the successful validation runs.
- A single lot acceptance cleaning validation might be possible if a product is manufactured infrequently (e.g. one time a year) or a clinical trial lot is run temporarily in product equipment.



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Cleaning run success



•A validation run is deemed acceptable when the equipment is both visibly clean and meets the acceptance criteria for product residues and cleaning agents at the first sampling without additional cleaning required.

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Interim documentation and final package

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Interim reports

- Interim reports must be approved by the cleaning subject matter expert and the Quality Unit.
- The validation interim report should include at a minimum the following:
  - Summary of the activities
  - Analytical test results
  - List of all discrepancies and resolutions
  - Conclusions and recommendations
  - Approval page



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Final validation package

The final cleaning validation package recollects:

- A summary of the cleaning protocol
- All executed protocols and revisions
- Data from all cleaning runs
- Copies of cleaning records and/or procedures
- Routine monitoring of cleanliness after validation
- Conclusions regarding the cleaning validation process.
- Approval page



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STERIS
Life Sciences

Stage 3: Continued Process Verification

Science & Solutions for Life

Monitoring and data trending



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Process monitoring

- Includes collecting and interpreting cleaning data to detect undesired variability.
- Routine or periodic sampling must be specified and recorded.
- Type of sampling, number of samples, sampling frequency, and analytical tests varies per cleaning method.
- Examples:
  - Non-specific analytical methods
  - Rinse sampling



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Process capability

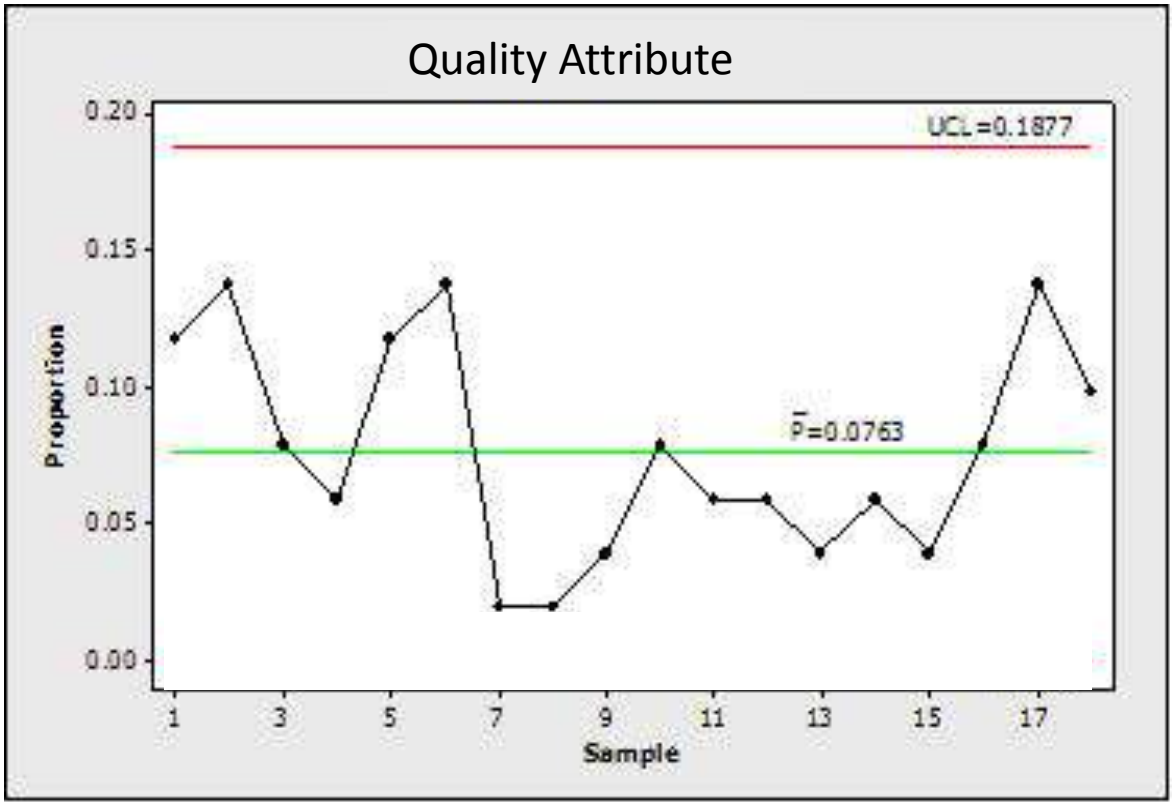
- Compares the output of an *in-control* process to the specification limits by using *capability indices*.

$$\mathrm{Cpk} = \frac{USL - \mu}{3\sigma}$$

Where:
Cpk = Capability index
USL = Upper Specification Limit
μ = average of the measurements
σ = standard deviation of the measurements

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Process capability chart



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Process analytical technology



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FDA Guidance to PAT

- September 2004, the FDA released the PAT Guidance for the Industry.
- PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements, process understanding, and process control.
- PAT in cleaning may be applied to complement cleaning validation and later on to support continued verification.



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PAT in cleaning applications

•Bader, K., Hyde, J., Watler, P., and Lane, A. (2009) Online total organic carbon (TOC) as a process analytical technology for cleaning validation risk management. Pharmaceutical Engineering. January/February 2009 pp 8-20.

•Verghese, G and Lopolito, P. (2007) Process Analytical Technology and Cleaning Contamination Control, Fall 2007. Pp 22-26.



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Preventive maintenance



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Periodic maintenance check list

- Must be set-up on a regular schedule.
- These may include calibration of:
  - weight measurement devices
  - thermometers
  - flow meters
  - conductivity meters
  - pH probes
  - and other measuring devices and testing equipment utilized in the cleaning process
- These schedules should be set up in advanced for all critical equipment and instruments.



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Remediation procedures

- Identification of surface imperfections:
  - rouge
  - scratches
  - crevices
- Surface abnormalities should be noted during routine visual inspection.
- Procedures should be in place to rate the severity of the abnormality and determine the corrective action if needed.
- Periodic check of worn gaskets and O-rings.



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Derouging and passivation

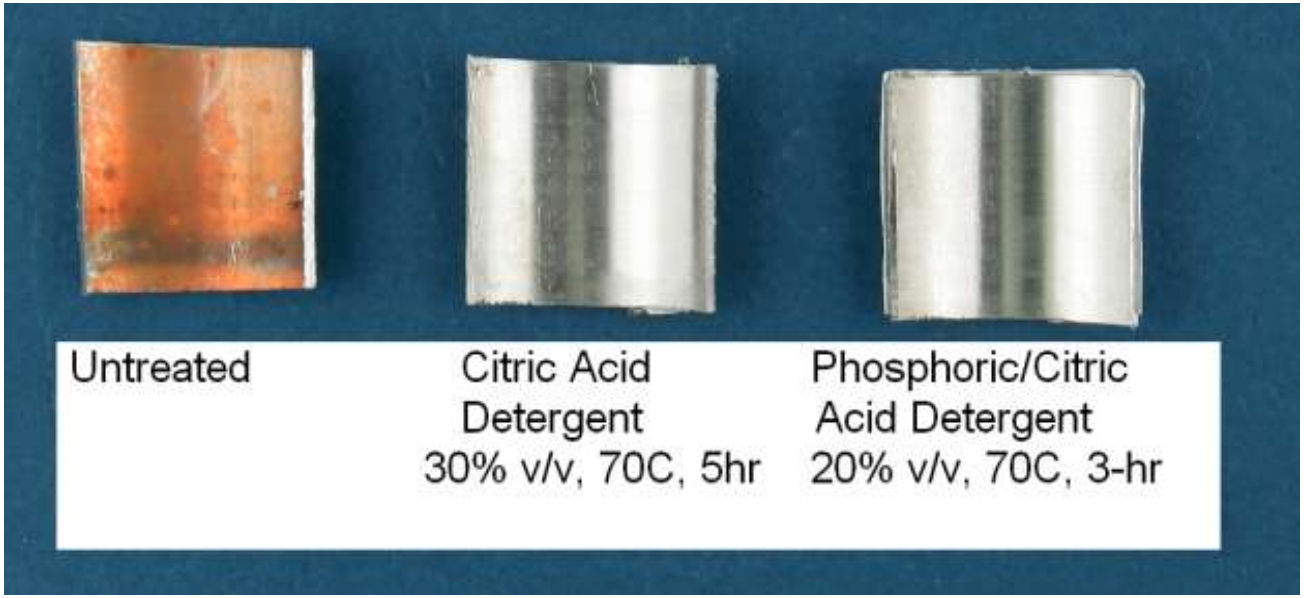
- Derouging
  - Various types of rouge (Type 1, 2, 3)
  - Derouging process may depend on type of rouge
  - Alkaline cleaning followed by acidic cleaning recommended using approved chemistries
- Passivation
  - Ensure formation of Cr enriched layer with adequate Cr/Fe ratios



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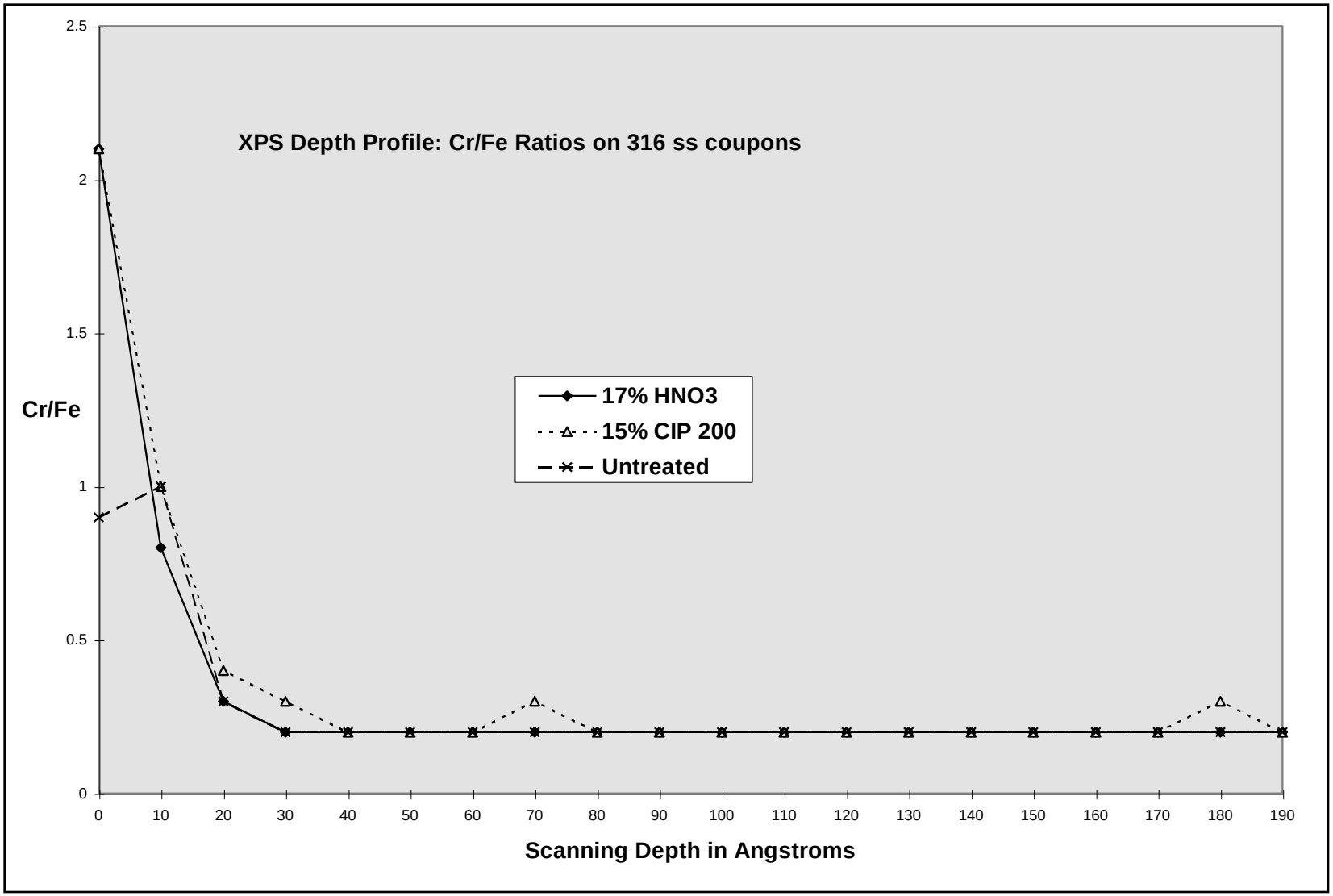
Derouging case study

Pipe pieces from a purified water system:



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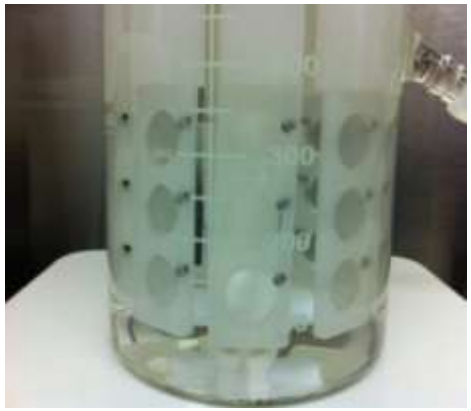
XPS depth profile



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Biofilms

- Community of microorganisms encased in self-produced matrix of extracellular polymeric substance (EPS).
- Cleaning with alkaline detergents with oxidative mechanisms followed by antimicrobial agents is effective against specific microbial organisms.







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Periodic review and retraining

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Re-training

- When to retrain:
  - Process change
    - Clarification
    - Modification
    - Improvement
  - Deviation
  - Regular schedule



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Periodic review

- Cleaning procedures should be periodically
  - typically every 2 -3 years
- The periodic reviews may consist of minor editorial changes to ensure that instructions are clearer to the operator.
- Additions or deletions to the SOP must not significantly alter or change the current validated procedures.



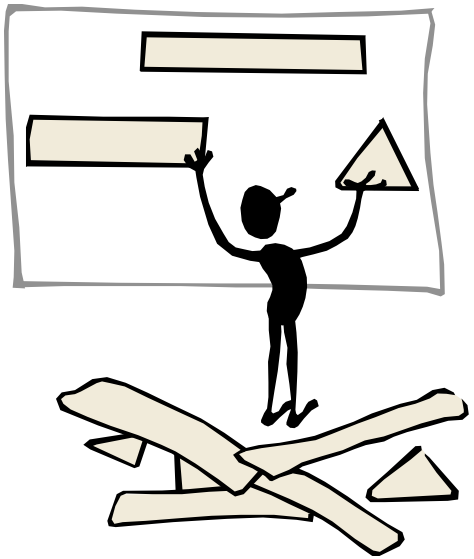
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Change control procedures, deviations, OOS, and CAPA

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Change control

- Change?
  - Inadvertent
  - Planned
- Examples
  - Pump failure
  - Change in cleaning agent
  - Change in water quality
  - Change in equipment surfaces
  - Change in manufacturing method
- Key: evaluate and document



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Process deviations

- Deviation once cleaning process is validated
- Examples:
  - Wrong cleaning agent or wrong cleaning agent concentration used
  - Not visually clean after cleaning
  - Equipment failure during cleaning
  - Manufacturing process deviation
  - Exceed hold time



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Possible causes of excursions

- Application conditions
  - Time
  - Temperature
  - Application method
  - Personnel
- Residue sources
- Monitoring technique
- Cleaning agent (concentration, quality)
- Water quality
- Equipment failure/malfunction



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General approach

- CAPA (Corrective and Preventive Actions)
- Corrective: Fix what’s wrong
- Preventive: Take steps to make sure doesn't happen again
- Requires investigation to find root cause



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Investigation

- Changes in
  - Manufacturing process
  - Cleaning process
- Attributable causes
- Effects of deviations
- Corrective / preventive actions
- Increased monitoring
- Documentation



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Corrective action?

- Consequence of failure depends on when discovered
- Remember cleaning failure ordinarily only affects release of equipment for subsequent product manufacture



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Corrective action? (2)

- If detect *before* next product manufactured, can limit corrective action to making sure equipment is suitably clean for release
- May involve recleaning and/or retesting



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Corrective action? (3)

- If detect *after* next product(s) manufactured, major focus of corrective action is making decision on disposition of that next product(s)
  - Release or destroy?
- Still need to investigate equipment to see if any additional cleaning and/or testing is required



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Failure in protocol?

- With any failure during protocol execution, must consider effect on validity of that protocol run
  - Invalid run
    - Keep out of the consecutive criterion
  - Suggestion of process insufficiency
    - Improve and start over



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Sampling issues?

- Sample lost or compromised
- Sample just not taken
- Swab resampling may be appropriate (but not rinse)
- Rationale for why not affect protocol
  - Representative surface vs. worst case swabbing location
- May treat as invalid run



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Recleaning?

- In all cases consider the need to reclean and test equipment before use for next protocol
- Recleaning is generally something I recommend for even for a successful protocol execution
  - Due to possible issues related to contamination during sampling



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Failure after validated?

- With any failure during routine manufacture, must consider:
  - Effect on subsequent product
  - Effect on process “state of control”
  - Need for change control



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Revalidation vs. continued process verification



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Ongoing control

- Evaluation on “regular” basis
- Includes review of:
  - Change control data
  - Monitoring data
  - Deviations
  - Corrective and preventive actions
  - Maintenance
  - Quality records
  - Training
  - Validation report



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Ongoing control (2)

- If review shows control and consistency, can summarize investigation and conclude process is still validated.
- If review shows inconsistencies and lack of control --
  - Review cleaning process to improve
  - One or more PPQ runs to confirm



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Ongoing review

- Previously done on a yearly basis
  - Documented with summary report
- Now emphasis on continuous evaluation to assure “state of control”
  - System for detecting unplanned departures
  - Trending, to detect process drift
  - Detect new unexpected sources of variation
  - Review by trained personnel



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Repeating PPQ runs

- Not a requirement
- May be done on a regular schedule
- May be done more frequently initially
- May be only one PPQ run, involving less sampling than was done initially
- Objective is to discontinue this type of monitoring



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Human Drug CGMP Notes

STERIS Life Sciences

"Once cleaned by a validated procedure, a firm generally should not be expected to analytically examine equipment surfaces to demonstrate cleanliness…. Hand cleaning methods may be an exception…. Usually visual inspection of surfaces, including hard to clean nooks and crannies, along with rinse water testing would suffice." (9:2)



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Revalidation?

- At least for the FDA, revalidation is no longer a useful term.
- If make a significant change, are not revalidating the old process but validating what is a new process.
  - Not to say that can't depend to some extent on appropriate data from old process to help provide assurance of control for new process
- May or may not require IQ/OQ



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Manual methods

- PIC/S Recommendations: “manual methods should be reassessed at more frequent intervals”
- Human Drug CGMP Notes (2001): “Once cleaned by a validated procedure, a firm generally should not be expected to analytically examine equipment surfaces to demonstrate cleanliness…. Hand cleaning methods may be an exception to this general rule because of inherent variability in operator compliance and abilities.”



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Manual methods (2)

- In addition to yearly cleaning validation review, consider one validation run
- Does not have to be for every product
- Challenge is the operator, showing consistency
- If manual cleaning processes are similar, pick one product/process as representative, and perform protocol run for that one



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Summary

- Consider your objectives in routine monitoring
- Select appropriate data to collect to demonstrate a “state of control”
- Set action and/or alert levels
- React and trend monitoring data
- Change control program
- CAPA program
- Include in regular review process
- This is part of “continued process validation”



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Questions and Answers

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