# The Life Cycle Approach to Cleaning Validation

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Presented by:

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Science & Solutions for Life

# Agenda

- Background
- Process Design
- Process Qualification
- Continued Verification
- Q&A

# Curriculum Vitae

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**Elizabeth Rivera** is a technical service manager for the Scientific Division of STERIS Corporation (Mentor, Ohio). Currently, she provides technical assistance in the areas of selection of detergents, disinfectants and sterilization assurance products including the application and use of these in the pharmaceutical, biopharmaceutical, cosmetics, medical devices, dietary supplements and related industries. In addition, she offers conferences and exhibits on educational technical forums such as *IPA, Interphex, ExpoFYBI, ETIF, PDA, ISPE, Expofarma, OMICS, Executive Conference* and more. Also, she has published articles related to cleaning and microbial control. She has a bachelors and masters degree in Chemical Engineering from the University of Puerto Rico. Elizabeth has over 10 years of experience and travels to places in North America, Latin America and elsewhere to support customers in various aspects of cleaning and decontamination. Previously, she held positions at pharmaceutical companies. She has extensive experience in cleanup of active pharmaceutical programs.  Visit her profile. in ©

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# Background

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# Traditional Approach to Validation

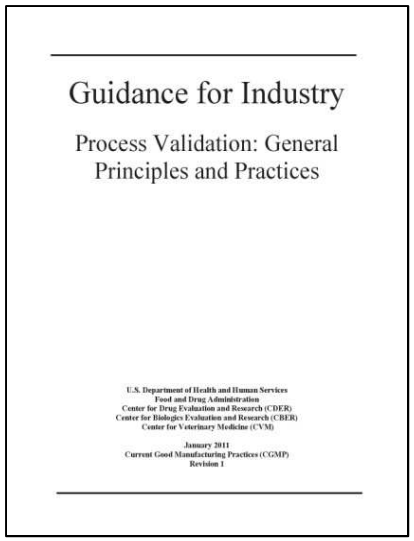
- Documented evidence at commercial scale (protocols)
- High level of assurance (data/reports)
- Consistency (minimum of 3 lots)
- Pre-established quality attributes (acceptance criteria)
- Summary and package closure

DESIGN **>>> VALIDATION >>>** MONITORING

# New Validation Approach

**US FDA Process Validation Guidance** (2011):

- Process validation: data collection and evaluation through a design phase and commercial production which establishes scientific evidence that a process will consistently provided expected results.
- Includes traditional concepts
- Adds the “life cycle” approach


Guidance for Industry

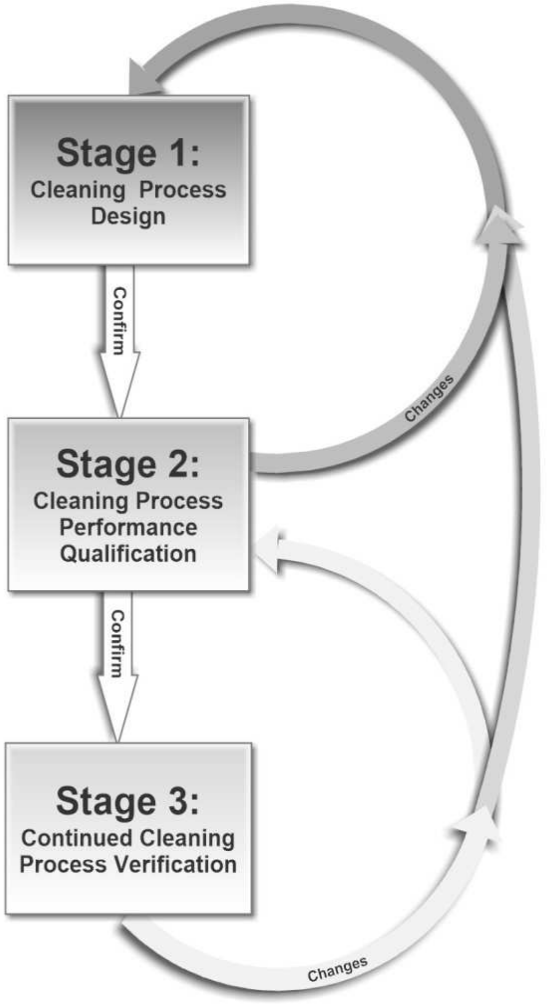
Process Validation: General Principles and Practices

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

**DESIGN >>>** VALIDATION **>>> MONITORING**

# Life Cycle Approach to Cleaning Validation




***Cleaning*** is a type of Process:

- 1: Design (development)
- 2: Qualification (reproducibility)
- 3: Continued verification (validation maintenance)

# Objectives

- New vs. Old Approach
  - Same underlying questions
  - How clean is clean?
  - How can we prove it is clean?
- Restructure cleaning validation concepts under new approach
- Capture some consequences of the new approach.

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# Stage 1: Cleaning Process Design

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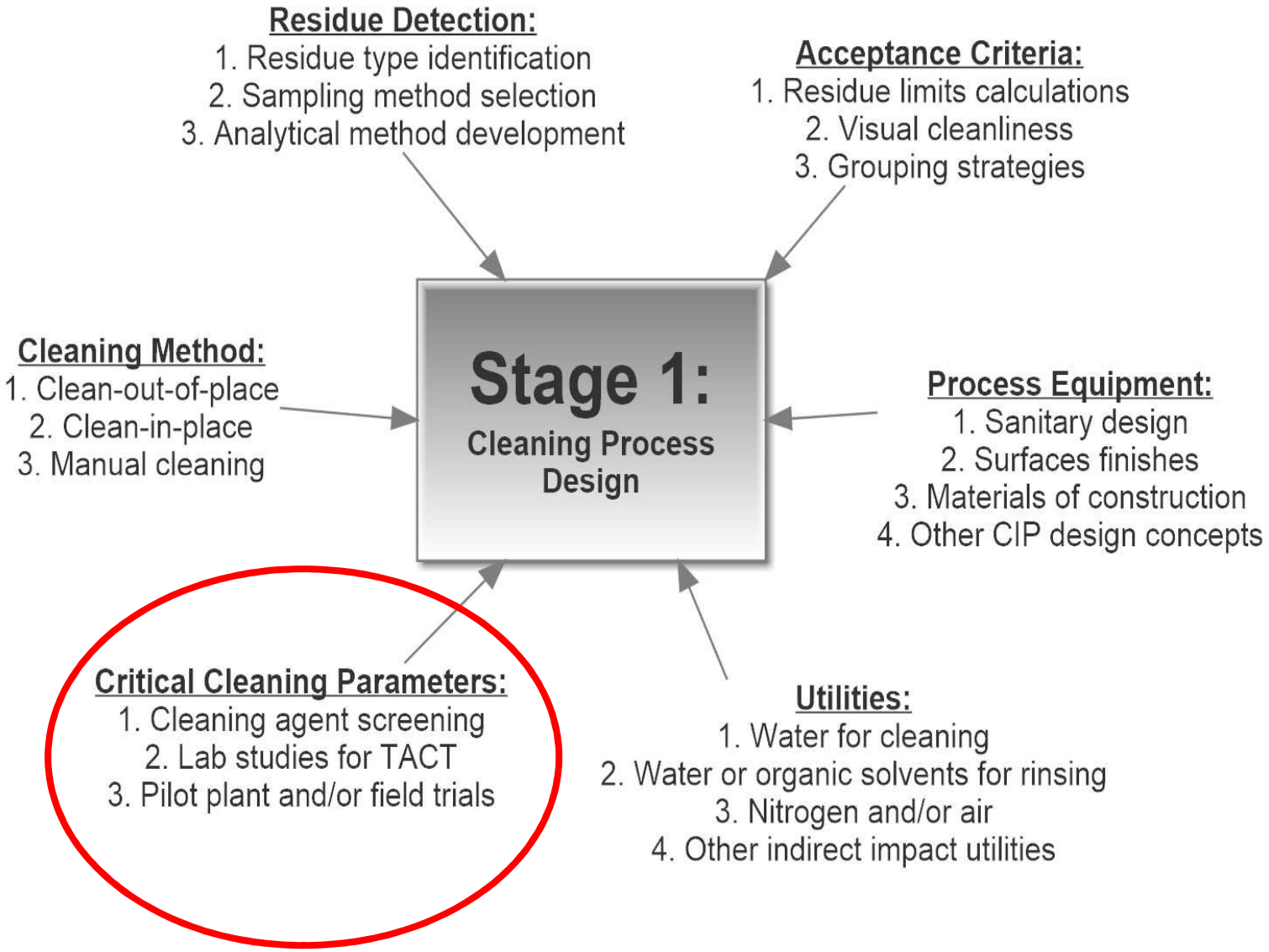


Ref: Lopolito and Rivera. PDA Contamination Control Book. Vol 2. 2014

# Emphasis on Design and Development

Understand your cleaning process:

- Determine sources of variability (parameters)
- Minimize their impact (operational range)
- Lab studies and pilot plant are useful.

# Laboratory Studies

- Selection of critical cleaning parameters
- “Stress” parameters
- Determine most difficult to clean soils from a group “worst-case”

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.


Water break free?

Weight change?

# Design Phase Documentation

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# Stage 2: Cleaning Process Qualification

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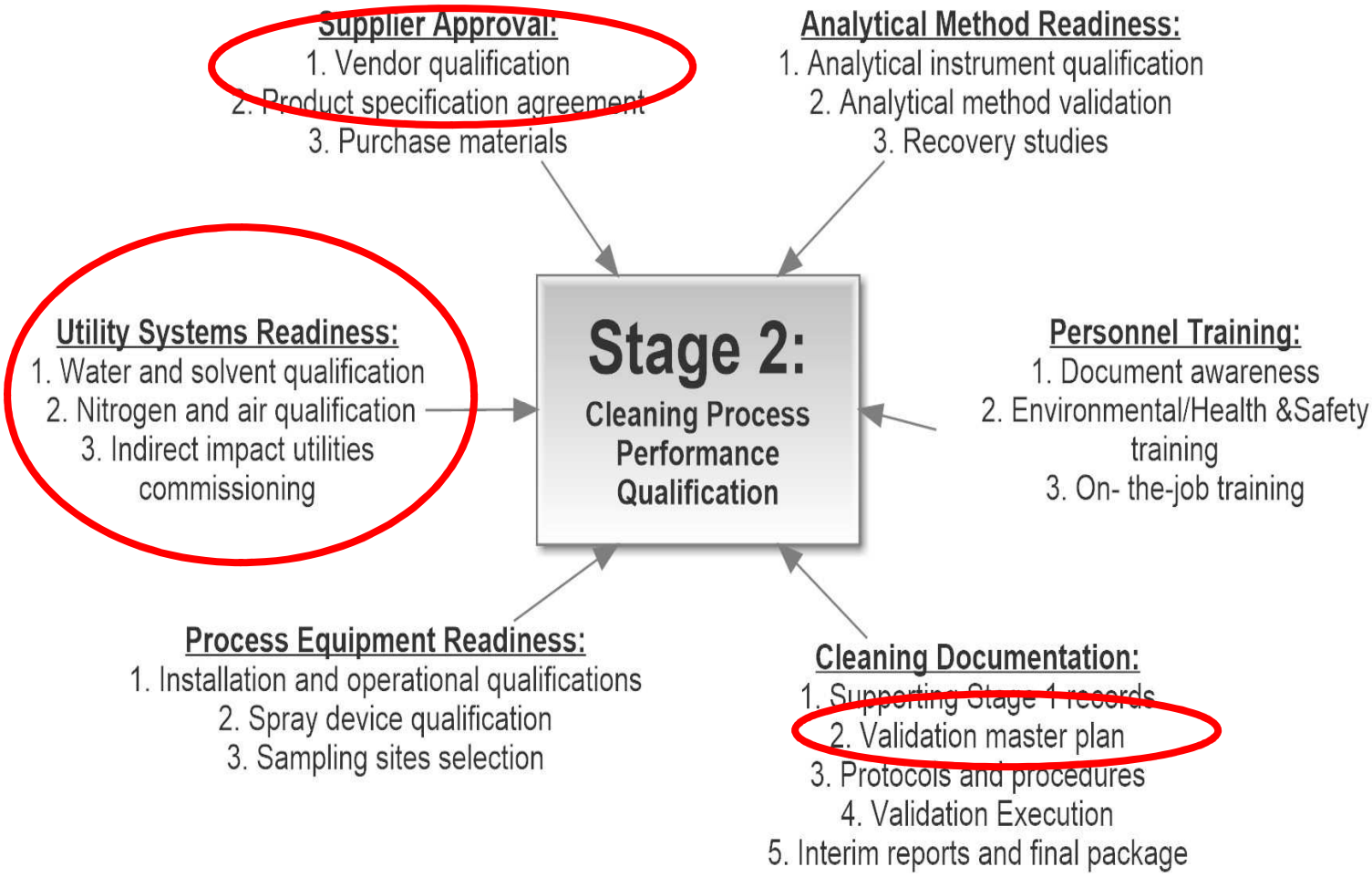


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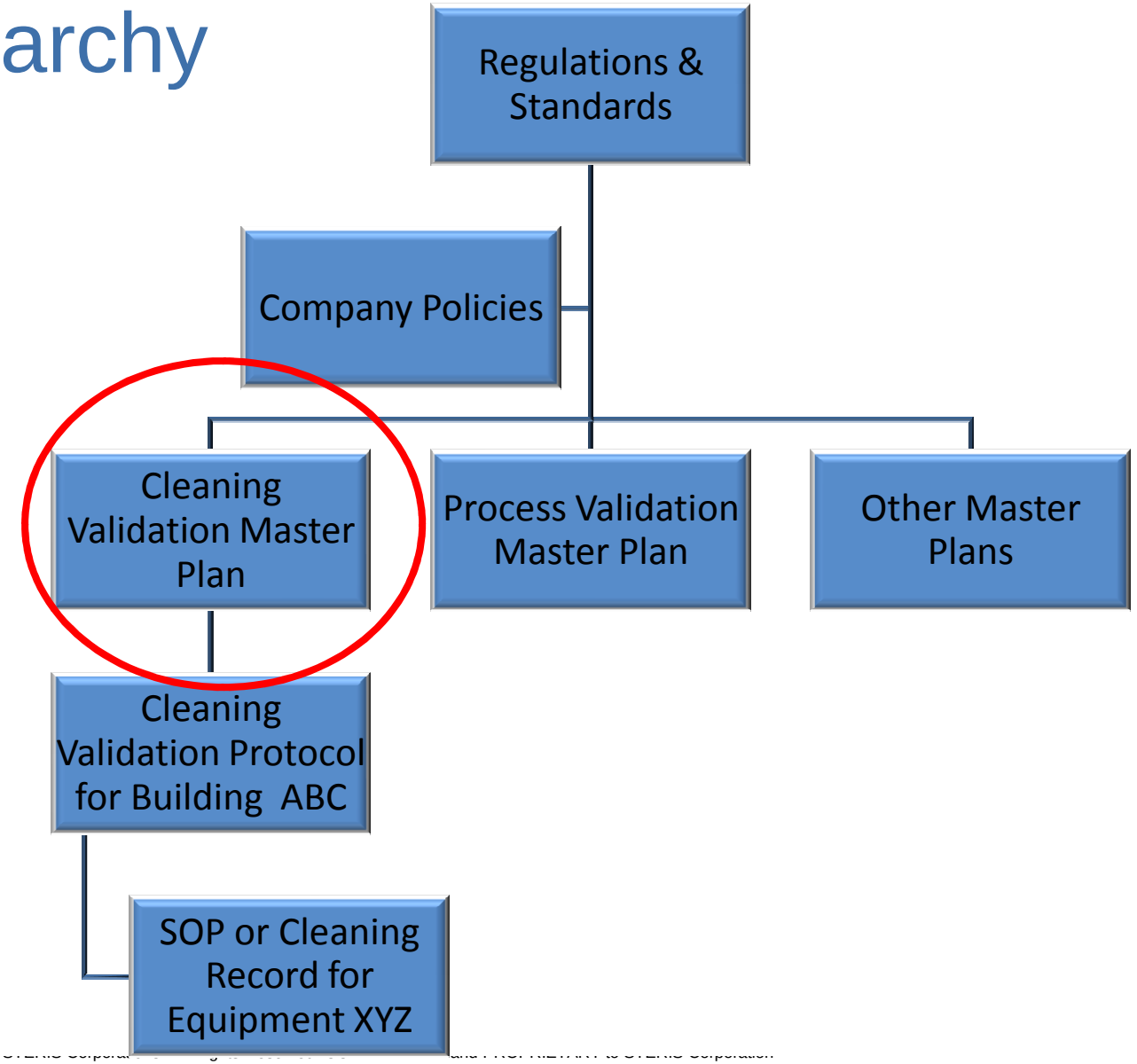
# Document Hierarchy



# Qualification Conditions

| Tradicional Approach | New Approach |
|---|---|
| •Validations runs under worst-case conditions (ex. Dirty hold time)<br>•Validation runs under normal process range<br>•Minimum three validation runs to show “consistency” | • Identify sources of variability<br>• Design a cleaning process that:<br>  ◦ Reduces variability<br>  ◦ Minimizes the effects of variability<br>• If robustness is demonstrated during design phase then there is no need to demonstrate during qualification. |

# Utilities Preparation

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- Utilities directly impacting cleaning must be qualified (IQ, OQ).

- Indirect impact utilities must follow at least good engineering practices.

# Supplier Qualification

- Cleaning and sanitization agents must be considered high impact processing aids.
- They must meet pre-established specifications
- They must be suitable for use in GMP applications
- Consequently, suppliers must be qualified and approved for use.

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# Stage 3: Continued Cleaning Process Verification

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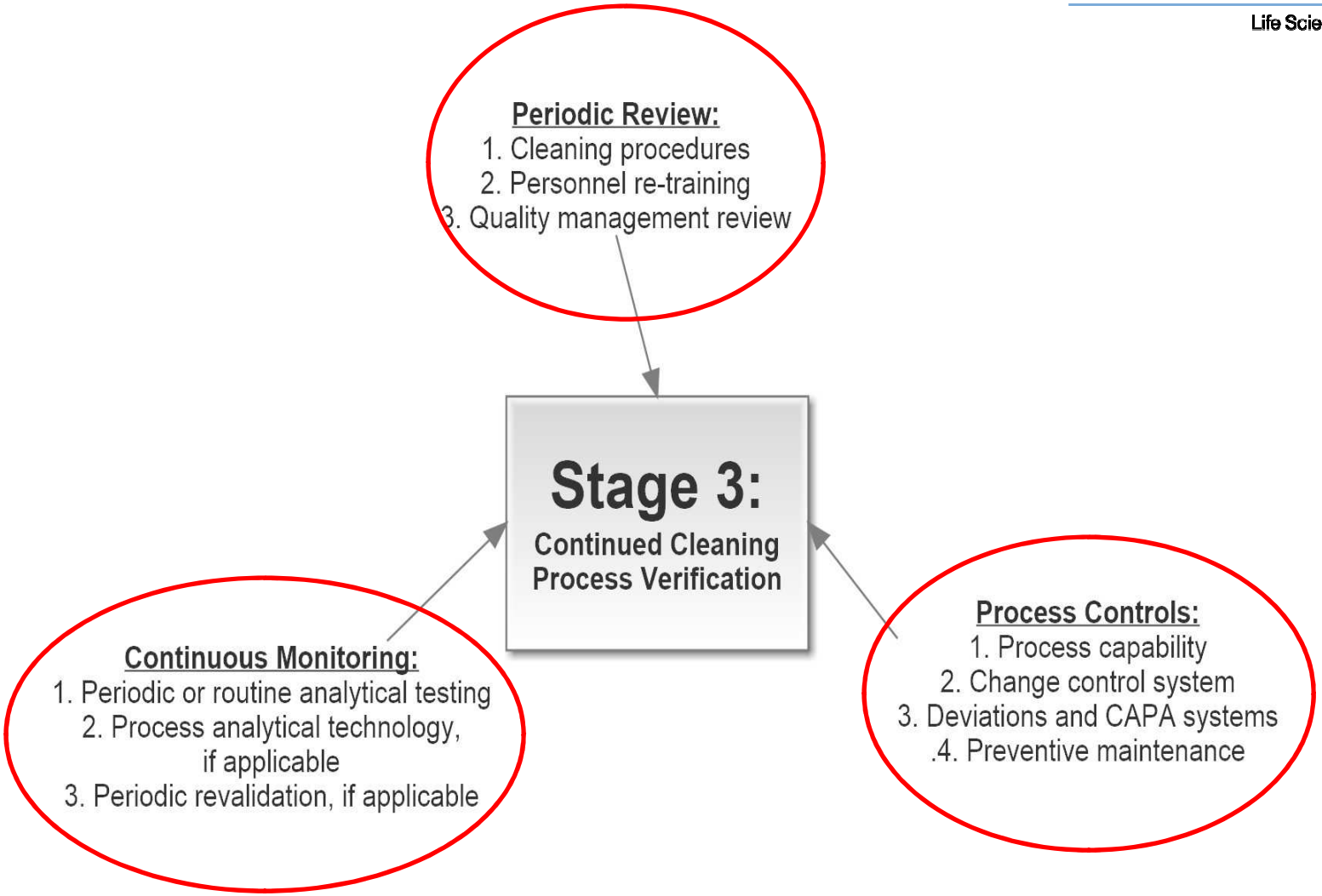
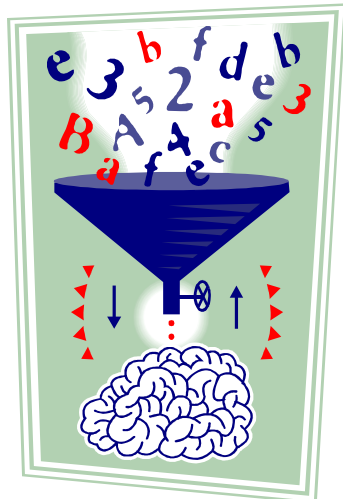



Ref: Lopolito and Rivera. PDA Contamination Control Book. Vol 2. 2014

# 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



# 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.

# 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.

# Remediation Procedures

| | Establish procedures for: |
|---|---|
| Surface | • Periodic derouging and passivation<br>• Repairing scratches, crevices and other surfaces imperfections per sanitary standards |
| Valves and sampling ports | • Approved valves and proper orientation<br>• Periodic gasket inspection and replacement per manufacturer recommendations<br>• Visual inspection of non-sanitary designs |
| Dead Legs | • Proper orientation and length to diameter ratio<br>• Periodic inspection to verify holes are not clogged |
| Spray Devices (automatic cleaning systems) | • Periodic derouging and passivation<br>• Repairing welding imperfections per sanitary standards. |
| Piping | • Periodic inspection and replacement of worn gaskets per manufacturer recommendations<br>• Periodic derouging and passivation<br>• Repairing welding imperfections per sanitary standards |
| Vessels | • Periodic inspection and replacement of worn gaskets per manufacturer recommendation<br>• Repairing welding imperfections per sanitary standards |
| Pumps | • Periodic inspection and replacement of worn gaskets per manufacturer recommendation |

Ref: Lopolito and Rivera. PDA Contamination Control Book. Vol 2. 2014

# Change Control

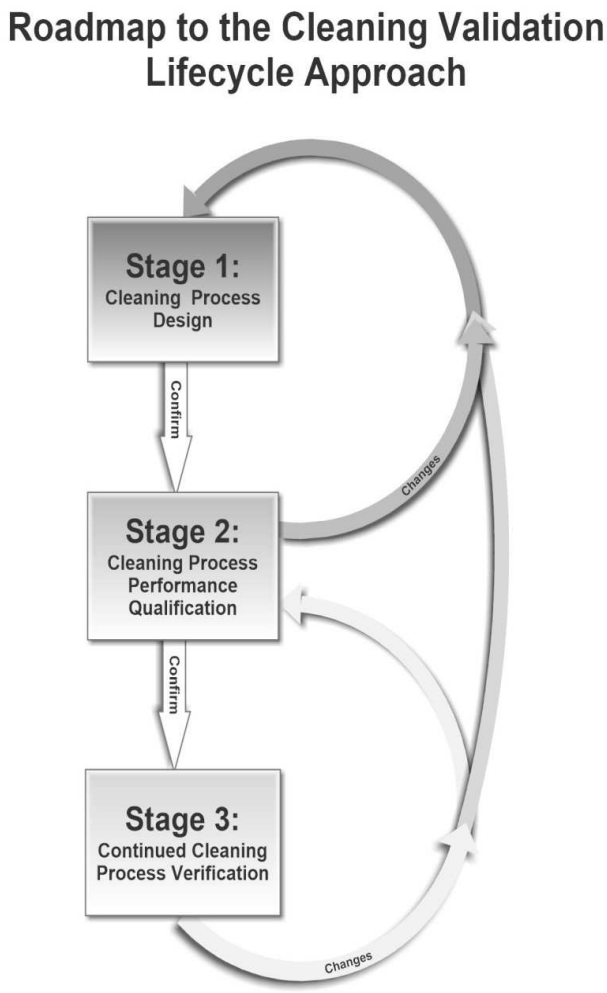
| Changes to | May Impact |
|---|---|
| **Detergent** | Cleanability of the soils |
| **Cleaning Parameters** | Cleanability of the soils |
| **Analytical Method** | Detectability and quantification of residues |
| **Equipment Design** | Surface coverage, equipment drainability, change over time |
| **Personnel** | Training and level of experience |
| **Dirty Hold Time** | Cleanability of soils, levels of bioburden |
| **Cleaning Hold Time** | Extraneous matter, bioburden |

# Ongoing Control

- Evaluation on “regular” basis
- Includes review of:
  - Change control data
  - Monitoring data
  - Deviations
  - Corrective and preventive actions
  - Maintenance
  - Quality records
  - Re-training
- If review shows control and consistency, summarize investigation and conclude process is still validated.

# How should we react to this?

- In theory, we should have always done all these.
- Main difference is definition and documentation.
- Primary goal is to have a good Design Phase that helps support decisions in the long run.
- Legacy products must have at least Stage 2 and 3.



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# Questions

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