

Maintaining Good Cleaning Practices

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The Cleaning Program Life Cycle



Cleaning Regulations

- FDA CFR Title 21 parts 210 and 211
- EMEA Annex 15
- EMEA Annex 18

- “ (a) Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. (b) Protection of the clean equipment from contamination before use.” 21CFR Part 211.67

Major Elements to Maintaining the Cleaning Process

- **Compliance with Standard Operating Procedures (SOP)**
 - ▶ Visual inspection of internal equipment surfaces prior to use
 - ▶ Conductivity verification
- **Maintenance Program for Equipment**
 - ▶ Preventative Maintenance Program (PM)
 - ▶ General upkeep of equipment
- **A Cleaning Monitoring Program**
 - ▶ Sampling
 - ▶ Critical parameters
- **A Revalidation Program**
 - ▶ Some or all elements of the original validation
- **A Revalidation Assessment Program**
 - ▶ Assessment of equipment to verify it is still in a validated state

Standard Operating Procedures

- **Effective Training of Operators**

- ▶ The SOPs must be robust and ensure that equipment is used in the manner it was validated.
- ▶ Operators must comply and perform the cleaning procedures as validated
- ▶ Eye exams
- ▶ Verification of training at a specified time increment
- ▶ Competency training to ensure operators understand the importance of maintaining the validated state

Visual Inspection

- **Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.**
 - ▶ EU Guidelines to GMP Volume 4
- **No residue to be visible on the equipment after cleaning procedures are performed**
 - ▶ Spiking studies to demonstrate level of visibility
 - ▶ Visual inspections conducted per SOP
 - ▶ Basically is it clean or not

Cleaning Process Record Keeping

- **Records must be kept showing the equipment numbers, the date of cleaning, who cleaned it and who inspected/tested it.**
- **Operators are Important**
 - ▶ They verify that it passes other analytical testing such as conductivity
 - ▶ They verify the equipment is visually clean
 - ▶ They should be the ones to notice a change in the internal surfaces.
 - ▶ They can recommend changes to the procedure
 - ▶ They have the most contact with the equipment

Failure Example

- **Failure to clean and maintain equipment and utensils used in the production of drug products in order to prevent contamination [21 CFR § 211.67(a)].**
- **For example, deteriorating equipment was observed, including: tape flaking off filling equipment directly above an uncovered hopper containing product to be filled, a leaking gasket in the product transfer line during filling, and two leaks in the Purified Water system. While your response appears adequate, we are concerned about the condition of your manufacturing facility in that during the inspection our investigators observed multiple conditions of disrepair.**

Preventative Maintenance (PM)

- **Scheduled for defined intervals**
- **Inspection of equipment for wear**
- **Replaces items such as gaskets, diaphragms, valves, etc as necessary**
- **Ensures that the equipment is mechanically sound prior to use**
- **Inspection of spray devices**

Failure Example

- **Utensils and equipment that directly contact sterile API during transfer are inadequate to ensure that these APIs are maintained sterile and pyrogen-free. For example:**
 - ▶ Several pits/holes were observed in the weld at the end and there was a crack observed between the handle and the end. These holes and crack create a challenge for sterilization.

What is Monitoring?

- **Monitoring refers to the routine measurements taken on the cleaning process that serve as indicators of whether the process is in a state of control (or considered from the opposite point of view, serve as indicators that the process either is not or may not be in a state of control).**

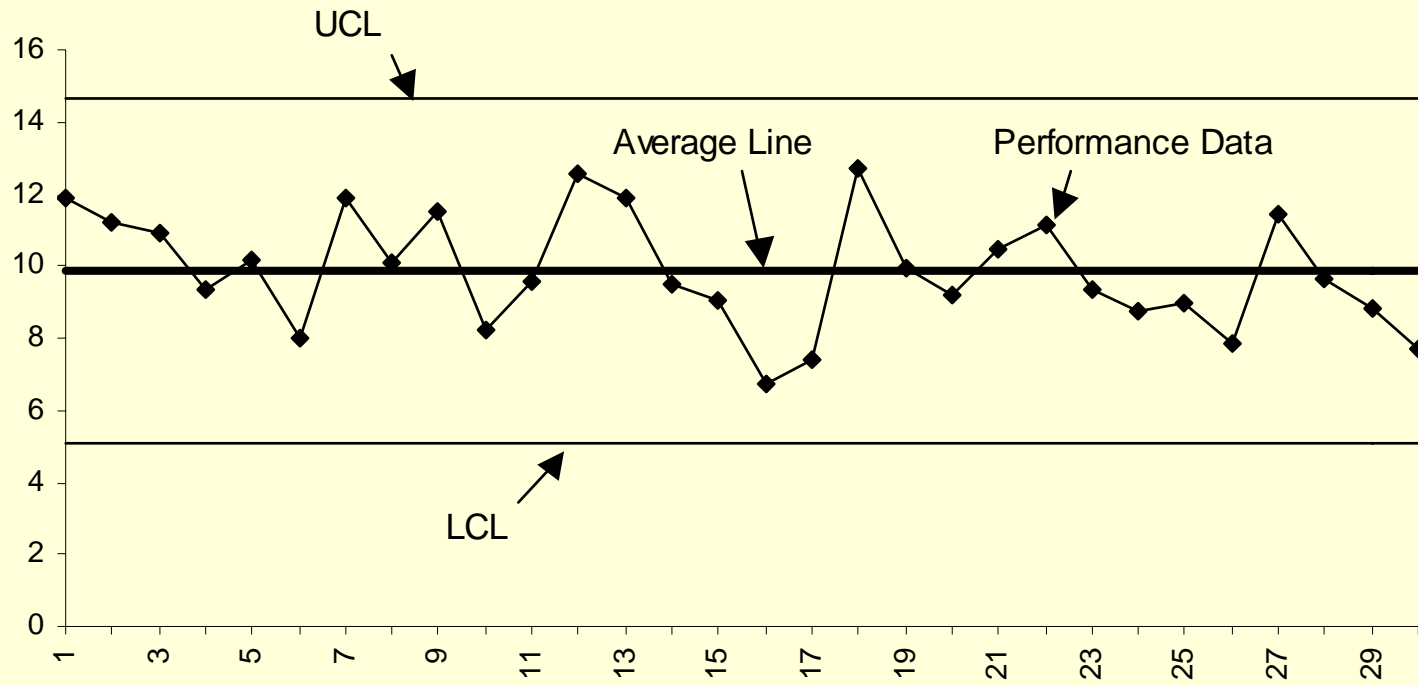
Why Monitor the Cleaning Process?

- **Control over a cleaning process can be demonstrated by a review of all relevant data at specified time increments.**
 - ▶ Relevant data includes sample results and trending of those results.
- **Monitoring the cleaning processes ensures the process is performed correctly and also provides an early warning if it is not performing as validated.**
- **Provides additional reassurance to the visual assessment and conductivity verification that is performed with each cleaning.**
- **Consistent with the lifecycle approach to validation (Design, Formal Validation Studies, and Ongoing Controls) as well as continuous improvement for manufacturing quality and efficiency.**

Monitoring Cleaning Cycles

- **Temperature, flow, pressure, fluid level, drainage, cleaning agent concentration, conductivity, and pH may play a role in monitoring the cleaning program.**
- **The nature of the cleaning method will determine the critical parameters to be monitored during cleaning.**
- **Instrumentation for monitoring critical parameters should be accurate and subject to a routine calibration program.**

Data Analysis



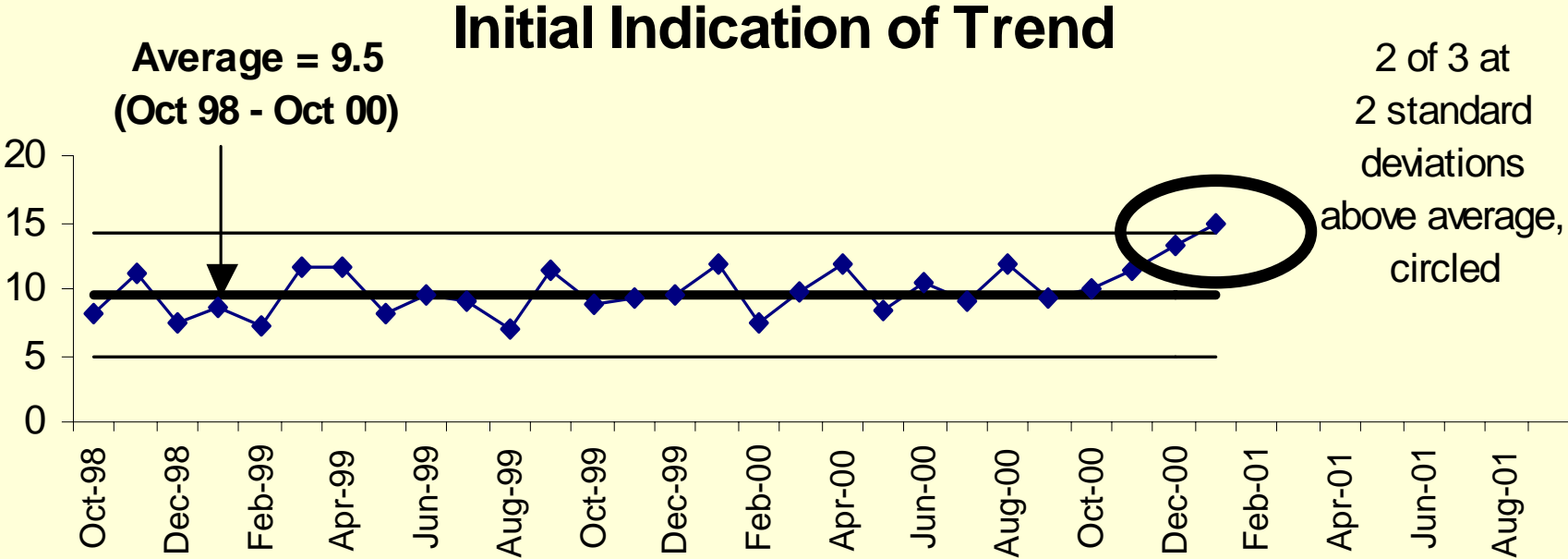
Identifying Trends

- **One point outside the control limits**
- **Two out of Three points two standard deviations above/below average**
- **Four out of Five points one standard deviation above/below average**
- **Seven points in a row all above/below average**
- **Ten out of Eleven points in a row all above/below average**
- **Seven points in a row all increasing/decreasing.**

Trending

- **In all cases, trends should be investigated to determine the special cause(s)**
- **A circle or a shift in the baseline is a trend**
- **Generally, short term shifts are left circled, long term shifts have a new baseline**
- **Remember – the goal is Prediction of Future Performance**

Trend Identification



Identifying a Trend

- **Report the trend**
- **Search for Special Causes**
- **Compare detailed data during the trend to previous stable time interval**
- **Consider Corrective Action Management necessary steps**

Monitoring Cleaning Cycles

- **Options for monitoring**

- ▶ Periodic Sampling (TOC, Bioburden, Endotoxin, Conductivity)
- ▶ Monitor Critical Operating Parameters (temperature, flow, pressure)
- ▶ Monitoring can occur using equipment that is in-line or off-line but ensure that it is accurate and in a routine calibration program.
- ▶ Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production.
- ▶ Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible.

Automated vs. Manual Cleaning

- **Automated Cleaning**

- ▶ May not require on-going verification if the system is designed, installed, and validated appropriately

- **Semi-automated Cleaning**

- ▶ Dependent on the reproducibility of the system

- **Manual Cleaning**

- ▶ Periodic Verification Required
- ▶ Verifies how appropriate the training is and how well the operator can perform the cleaning
- ▶ Collected sample data should be analyzed

Verification vs. Revalidation

- **Verification**

- ▶ Performed as part of cleaning monitoring
- ▶ Sampling can be less aggressive
 - Fewer areas
 - Indirect vs direct sampling

- **Revalidation**

- ▶ Could require portions of the initial cleaning validation to be repeated
- ▶ Samples that are required can be more aggressive than verification (Rinse vs Swab)
- ▶ Can include aspects of both verification and validation
- ▶ May be triggered by a change to equipment or cleaning procedures

Change Control

- **May Impact all of the cleaning process**
 - ▶ Standard Operating Procedures (SOP)
 - ▶ Assay methods
 - ▶ Equipment
 - ▶ Detergents
 - ▶ Times
- **Any changes to items determined during PQ as impacting to the cleaning process must be evaluated and ultimately approved.**

Failure Example

- **SOP XXXX, was revised May 17, 2004 to remove the requirement for [redacted] after use/prior to cleaning if inactivation time and temperature requirements were met during the inactivation process. These new cleaning procedures were not validated to establish the impact of the changes on the cleaning process.**

Change Control

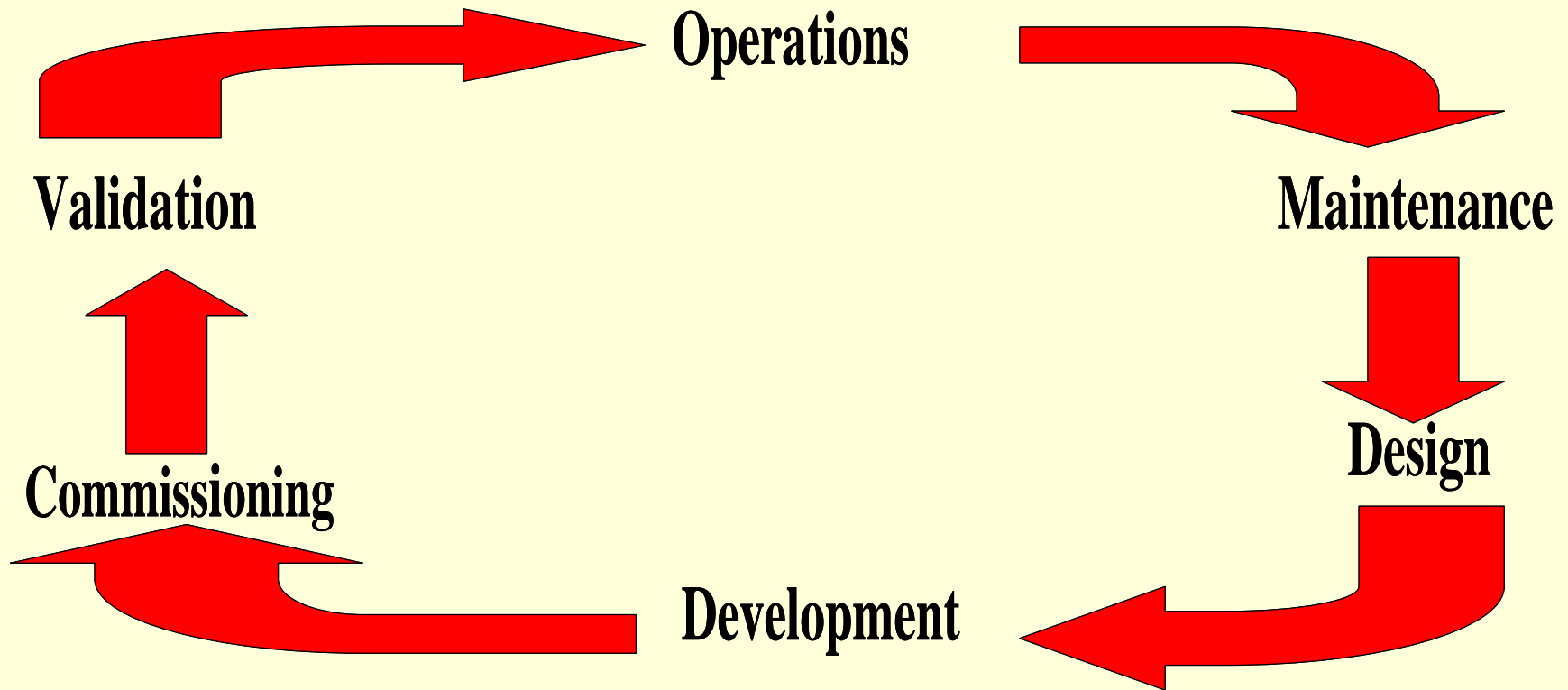
- **Changes must be pre-approved**
- **If the maintenance required is deemed a change**
 - ▶ The change control team determines the level of testing that is required
 - ▶ This could include
 - New cleaning samples (TOC, Conductivity, Bioburden, Endotoxin, etc)
 - Verification of flow rates
 - Confirmation of pathways
 - Verification of spray coverage
- **A validated process can be easy to maintain if an efficient and effective change control program is in place.**

Revalidation Assessment

- **Paper Exercise**
- **SOP Governed**
- **Frequency Based on Rationale**
 - ▶ Criticality of the equipment could determine if its assessed annually or every three years, for example.
- **Assessments Can Include**
 - ▶ Review of open and closed work orders
 - ▶ Review of related change controls
 - ▶ P&ID walk down of equipment
 - ▶ Review of related SOPs for updates that could affect the validated state
- **Assessments provide reassurance that the equipment has remained in a validated state.**

Summary

Cleaning Program Lifecycle



Summary

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Thank you!!



Questions????