

Contamination Control “Cleaning Validation”

Ravi Hattarki
Manufacturing Projects Manager
CSL Behring, Australia
17th June 2014

This presentation will discuss

- Cleaning
- Potential Contaminants
- Regulatory requirement / expectation
- Challenges associated with Cleaning
- Cleaning validation Program and planning
- Continued Process Verification (CPV)
- Conclusion

Why clean?

- Cleaning is performed to remove product and non-product contaminating materials which could effect patient health &/or the quality of medicines
- Effective cleaning is an essential component of QA and GMP and patient safety
- Ineffective cleaning can lead to adulterated product, which can be contaminated by the previous product, by cleaning agents, and by other extraneous materials introduced into, or generated by, the process

Potential contaminants

- Airborne particulate matter
- Dust
- Lubricants
- Product residues
- Decomposition residues
- Cleaning agents
- Micro organisms and Endotoxins
- Operator interface

Cleaning and Regulatory Requirement

Why is there so much focus on cleaning from the regulatory agencies?

- In the manufacture of medicinal products and API's, the cleaning of facilities and equipment is an important measure to avoid contamination and cross contamination
- In compliance with the GMP regulations, cleaning is performed and documented according to the described procedures
- Regulatory expectation
 - (a) Historically, cleaning effectiveness was often monitored only visually
 - (b) However, residues of API's, excipients, protein degradation are increasingly an issue in inspections and audits

Cleaning and Regulatory Requirement

- Cleaning procedures has to be validated to satisfy the following agency requirements:
 - ❖ FDA published Guide to Inspections of Validation of Cleaning Processes – 1993
 - ❖ PIC/S Guideline to Validation – PI -006-3 (2007)
 - ❖ Annex 15 address cleaning validation in a separate chapter. Moreover, the ICH Guideline Q7 “GMP for APIs” also requires cleaning validation

What do regulators expect from a manufacturer?

- Bench scale or coupon studies to prove that the chosen cleaning process works and can be reproduced at full scale
- The following consideration should be given when designing a cleaning process:
 - *the solubility of the materials to be removed;*
 - *the design and construction of the equipment and surface materials to be cleaned;*
 - *the safety of the cleaning agent;*
 - *the ease of removal and detection;*
 - *the product attributes;*
 - *the minimum temperature and volume of cleaning agent and rinse solution; and*
 - *the manufacturer's recommendations*

Challenges

- Migration of bench scale studies to full scale within the facility is effective and can be reproduced
- Cleaning system and facility should be designed to avoid it being source of contamination and built up of dust & dirt
- Process equipment should be designed so that it can be easily cleaned throughout and can be reproduced

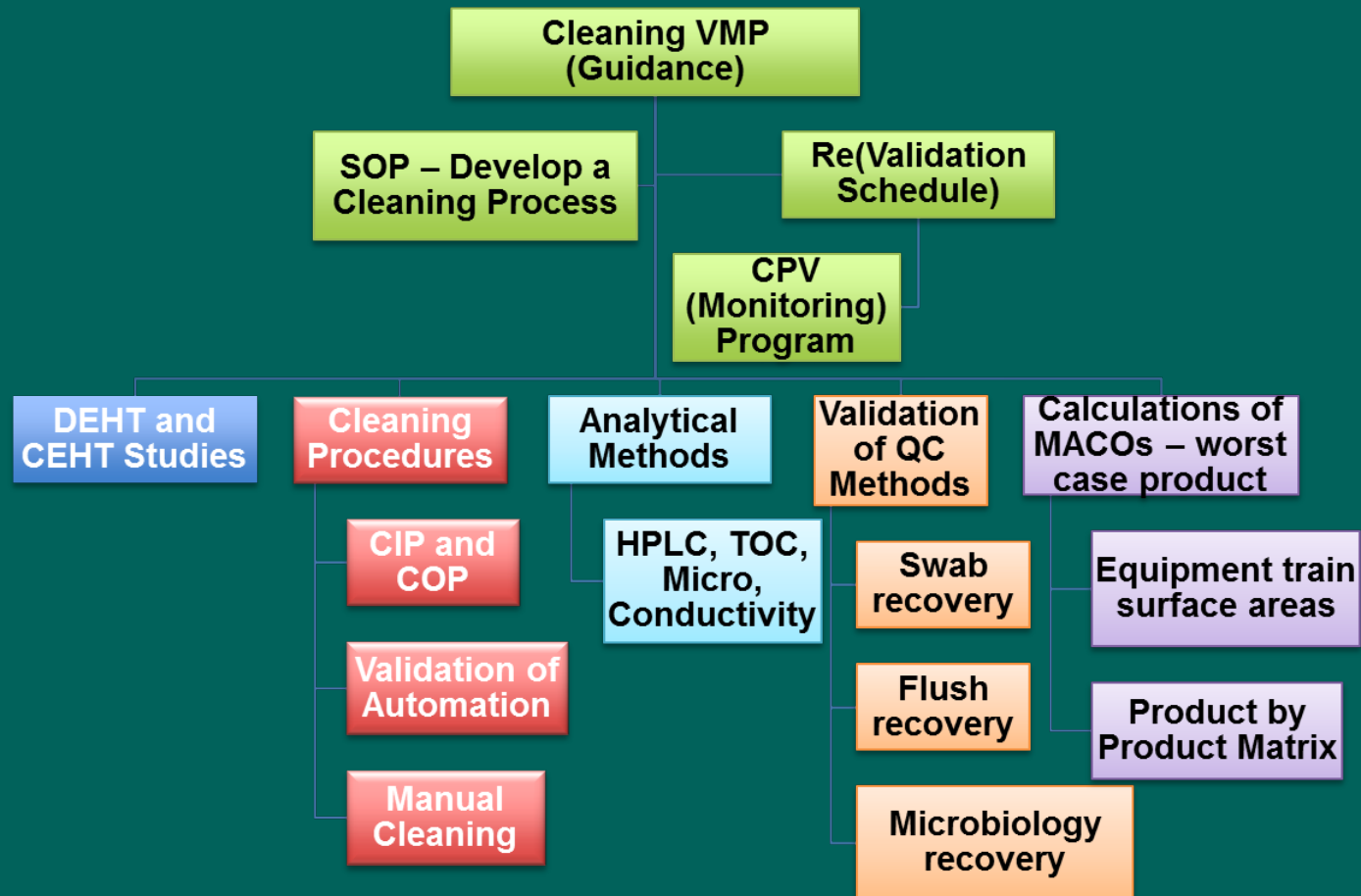
Challenges

- For biological a focus on viral inactivation steps and scale down/scale up to support clearance claims
- Evaluation of cleaning process related Critical Process Parameters (CPP's)
- Evaluation of cleaning related Critical Quality Attributes (CQA's)
- Cleaned equipment should only be stored in a clean and dry condition

Challenges

- Potential chemical interaction with non stainless steel surfaces (e.g. Gaskets, seals etc.)
- Carry-over of product, non product and cleaning agent residue
- Consideration for Dirty Hold Time and Clean Hold Times
- For manual cleaning process a well documented procedure must be in place
- Verification strategy (continued vs. continuous)

Scope of a Cleaning Validation Program



Validation Plan

- Validation Plan should include the following:
 - How clean is clean piece of equipment?
 - *Setting limits should have a sound scientific rational*
 - An in-depth risk assessment on the cleaning process
 - Prospective, Concurrent, Retrospective Validations as well as Re-validations
 - List of equipment (common vs. dedicated, Pre-VI vs. Post-VI)
 - List product manufactured using the same equipment
 - Product matrix

Validation Plan

- Clearly define product and Non product contact surfaces
- Worst case sampling location based on the equipment design
- If grouping strategy is applied, clear rational for this approach
- “Test until clean” not alternative to validation
- Usually minimum three consecutive successful PQ runs is acceptable, but its up to the organisation to decide (the end goal is to have a stable, reproducible process based on risk assessment)

Validation Plan

- Define CPP's and CQA's by risk FMEA based assessment
- Sampling / monitoring strategy
 - Surface Swab (for small or worst location) Vs. Rinse water (large area)
 - TOC Vs. Micro BCA
 - Testing for residual cleaning agent (conductivity or pH)
 - Endotoxin
 - Microbial
 - Visual Inspection
- Stability and recovery studies for TOC and Micro BCA test

Validation Planning

- Inclusion of Dirty Hold Time and Clean Hold Time
- Storage location and condition (must be dry and have minimal influence from the storage area) – preferably closed storage

Continued and Continuous Process Verification at CSL Behring

- Clean Group was formed in August 2012
 - The main objective were
 - Draw together site knowledge of cleaning technologies
 - Review the sites current control strategy in relation to potential contamination
 - Introduce changes to improve control over potential contamination
 - Strengthen the oversight of these controls
- Members who represent the Clean Group comprise of Subject Matter Experts from cross functional areas within the business

Why Continuous Process Verification

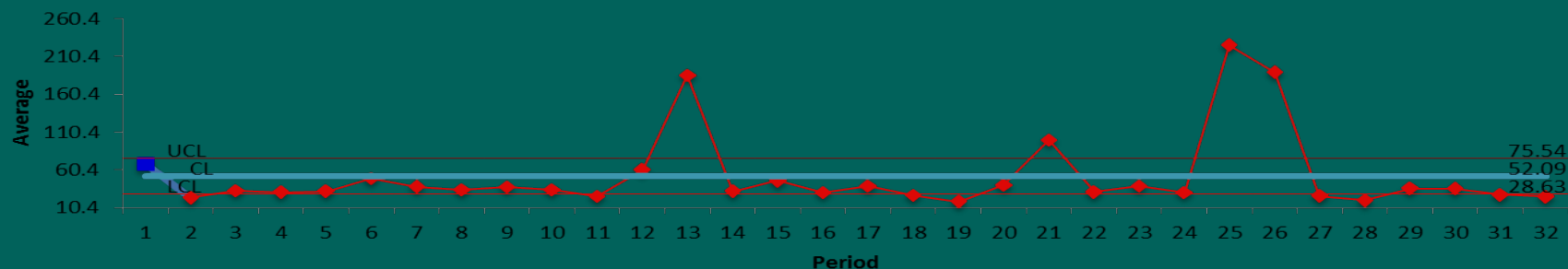
- Re-validation is disruptive and is generally concurrent – occurs semi – annually... raises risk if OOS occurs
- EMA and FDA Process Validation Guidance expects a CPV program for all production processes
- CPV programs provide significantly more information:
 - able to review trends
 - able to quickly make adjustments
- Use a quick turnaround method if possible eg.
 - Final flush sample (not swab)
 - TOC and conductivity, possibly bioburden
- CPV monitors selected CPPs and some CQAs

Example of a CPV Program

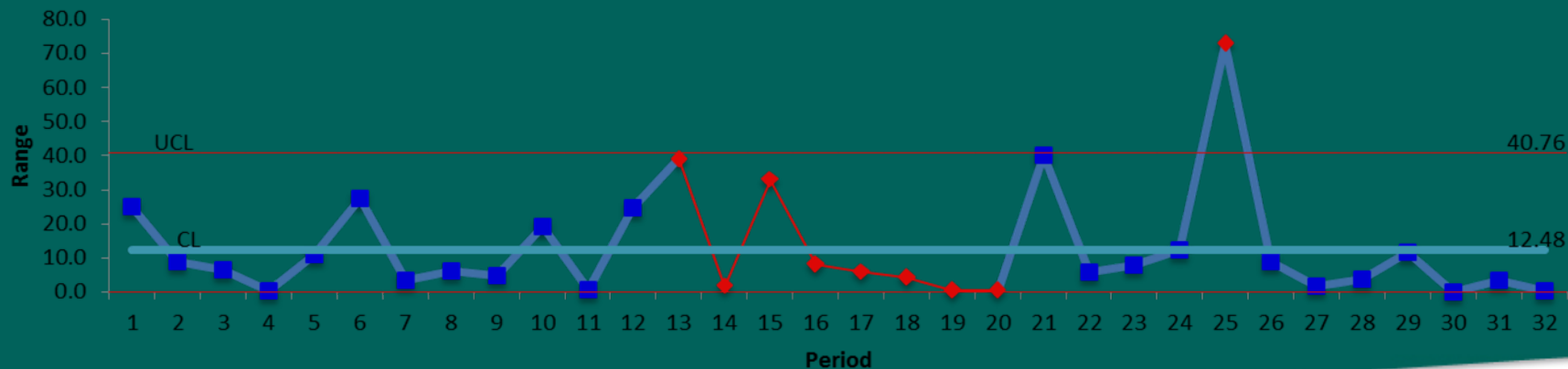
Critical Process Parameters CPP	Acceptance Limit
Dirty Equipment Hold Time (C)	Site Standard for portable tanks < 24 hours** Mandatory clean required at 48 hours**
Cleaning Agent Contact Time (C)	≥ 10 minutes per CIP path
Final Flush Temperature (C)	WFI ≥ 70 °C
Critical Quality Attribute CQA	Acceptance Limit
Microbial of Rinse Water (S)	Alert: > 1cfu / 100mL. Action: ≥ 10 cfu / 100 mL
Conductivity - in-line monitor (C)	Alert Limit > 2.0 uS/cm ² Action Limit >2.75 uS/cm ²
Conductivity flush (Lab Sample) (S)	Alert Limit > 2.0 uS/cm ² Action Limit >2.75 uS/cm ²
TOC of Rinse Water Flush (S)	Alert Limit > 275 ppb. Warning Limit > 500ppb. Action Limit: based on 1/100 MACO
Visual inspection equipment (C)	Visually Clean

Recent CPV Trend Data – April 14

Trend Chart



R XbarR Chart



Conclusion

- Cleaning validation is challenging
 - These challenges are further enhanced if a facility is used to manufacture multiple products
 - The manufacturing process can have multifactorial inputs which can make the cleaning process very difficult
- There is an increased focus from the regulators on manufacturing firms to ensure robust processes are in place to control contamination and is supported by scientific rationale
- Documentation and records is an important and essential part of compliance
- Continued process verification and trending provides a better understanding of cleaning processes than periodic re-validation

Acknowledgement

- Clean Group representative
Fergus Hawes, George Barlas, Bruce O'Regan and
Angela Hamrock-Fox
- Destin Le Blanc – Cleaning Validation Technology
(CVT)
- Steve Williams - Director at SWA Biopharm P/L
(Compliance by Design)