Changing Role of Toxicology within Cleaning Validation with Regards to Industry Trends and Regulatory Requirements

Dr. Wendy Haines, PhD, DABT, ASQ CQA and John VanBerschot

PharmEng Technology, www.pharmeng.com

Abstract

Many pharmaceutical industry cleaning programs do not meet current regulatory expectations, which has a global impact for products manufactured or marketed within Europe. Historically, Cleaning Validation residue limits had to be practical, achievable and verifiable according to US and European requirements. However, newer changes indicate that residue limits should be based on a toxicological evaluation due to a revised European requirement. This transformation potentially results in new acceptance criteria being generated and also complete re-validation of the cleaning program with an ultimate goal of patient safety. Whereas an older cleaning program that may have shared the same goal, likely had a different pathway, which may have included amongst others mass based or dosage -based carryover calculations. Modern cleaning programs primarily focus on patient safety. They must include health-based exposure limits that take into consideration the identification of hazards and the assessment of the dose-response relationships. This is done by utilizing a pathway that may include, but is not limited to, TTC (Threshold of Toxicological Concern) and/or carryover calculations which incorporate PDE (Permitted Daily Exposure) or ADE (Acceptable Daily Exposure).

Problem Statement

Modernization of cleaning programs will meet the transformed regulations. This will be accomplished by the utilization of health-based exposure limits and toxicological evaluations, which has a global impact on all cleaning programs for products manufactured or marketed within Europe, while maintaining US regulations.

$$\text{ADE}\left(\frac{\text{mg}}{\text{day}}\right) = \frac{\text{NOAEL} \times \text{Weight}}{\text{UF}_\text{C} \times \text{MF} \times \text{PK}}$$

$$\text{PDE}^{*}\left(\frac{\text{mg}}{\text{day}}\right) = \frac{\text{NOEL} \times \text{Weight}}{\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}}$$

* 1.5 µg/person/day for **TTC**

$$\text{OEL}\left(\frac{\text{mg}}{\text{m}^3}\right) = \frac{\text{PoD} \times \text{Weight}}{\text{UF}_\text{C} \times \text{TK} \times \text{MF} \times \text{V}}$$

$$\text{Swab}\left(\frac{\text{mg}}{\text{swab}}\right) = \frac{\text{ADE} \times \text{SB} \times \text{TA} \times \text{RF}}{\text{MDD} \times \text{SSA}}$$

$$\text{Rinse}\left(\frac{\text{mg}}{\text{L}}\right) = \frac{\text{ADE} \times \text{SB} \times \text{RA}}{\text{V} \times \text{MDD} \times \text{SSA}}$$

Conclusion

Three take-aways: aligning Cleaning Validation with toxicological evaluation, provide tools to meet regulatory expectations, implementing results in compliance and patient safety.

Procedures / Examples

Evaluate toxicity of biopharmaceuticals, therapeutic proteins, chemicals and active pharmaceutical ingredients.

- Determine potential for health effects, pharmaceutical cleaning limits, personal injury litigation support, worker's compensation assistance, product safety based on information provided by client.
- Acceptable Daily Exposure (ADE) - "safe" limits for product cross - contamination purposes (multipurpose manufacturing operations) under the ISPE RiskMaPP Model (µg of API/day)
- Permitted Daily Exposure (PDE) - "safe" limits for product cross - contamination purposes (multipurpose manufacturing operations) under European Medicines Agency (EMA) Guideline (µg of API/day)
- Occupation Exposure Limits (OEL, µg of API/m^3) - established for worker safety purposes and restrict the amount and length of time a worker is exposed to airborne concentrations of hazardous biological or chemical agents

Toxicological Assessments Include

- Hazard identification
- Critical effects
- Determination of No Observed Adverse Effect Level (NOAEL)
- Uncertainty Factors
- Modifying Factor
- Pharmacokinetic Adjustment(s)

Employee Safety Training

- Discuss proper Personal Protective Equipment (PPE)
- Pharmacological mechanism of action
- Target organ/systemic toxicity
- Review signs and symptoms of possible exposure

Alternative Paradigm / Viewpoint

Toxicological Evaluation and/or Contribution Recommended

Cleaning Validation Master Plan

- **Stage 1** – Cleaning Process Design and Development
  - Implementation Schedule
  - Define the Cleaning Process Approach
    - Cleaning Verification or Cleaning Validation – Cleaning Objective Defined
    - Matrix Approach for Products or Product Stages (Intermediates) – **Worst Case Residue Identified**, Worst Case Equipment Identified, **Hold Times (Clean, Dirty, and Sterile Stand)**
    - **Campaign Changeover Strategy, Based on Time and/or Number of Batches**
  - Design and Qualification of Equipment
    - Define Equipment Design – Identify Critical (Cleaning) Process Parameters – CPPs: **Cleaning Agent Selection**, Cleanability Study, Cleaning Process Recipe Development
  - Determine the Required Cleanliness
    - Identify Critical (Cleaning) Quality Attributes – CQAs: **Determine Acceptance Criteria**; **Health Based Limits**, MACO, **Toxicological Evaluation**, Cleaning Process Based Statistical Evaluation
  - Develop Cleaning Cycle and Analytical Methods
    - Confirm Critical (Cleaning) Process Parameters – CPPs: Determine Supporting Development Studies: Worst Case Residue, **Degradation**, **Inactivation**, Conductivity Curve, **Visual Residue Limit**
  - Analytical Method Verification or Validation
  - Confirm Critical (Cleaning) Quality Attributes – CQAs, and Provide Justification and/or Scientific Rationale for Acceptance Criteria
- **Stage 2** – Cleaning Process Performance Qualification (Cleaning Process Validation)
  - Generate and Execute Cleaning Process Validation Protocols, including CPPs and CQAs
  - Perform all required sampling; **Direct Surface Swab, Rinse, and Visual Inspection**
  - Determine or Challenge **Dirty Hold Time, Clean Hold Time, and/or Sterile Stand Time**
- **Stage 3** – Continued Cleaning Process Verification
  - Determine Routing Monitoring, including **Time Interval and Sampling Frequency** Schedule
  - Determine Statistical Approach for Trending of Cleaning Process Validation
  - Execute and Report Statistical Trending for Cleaning Process Validation
  - Generate Cleaning Validation Periodic Review Assessment
    - Statement of Confirmation of Cleaning Validation Effectiveness
    - Statement for Validated State of Cleaning Process

References

FDA 1993, Validation of Cleaning Processes, Guide to Inspections Validation of Cleaning Processes

FDA 2004, Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach

ICH Q3C(R5), Impurities: Guideline for Residual Solvents

European Medicines Agency: Guideline on setting Health Based Exposure Limits for Use in Risk Identification in the Manufacturer of Different Medicinal Products in Shared Facilities

EudraLex, Volume 4 GMP Guidelines, Annex 15: Qualification and Validation

ISPE Baseline Guide Volume 7, Risk-based Manufacture of Pharmaceutical Products

Dolan D.G. et al. (2005). Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. Regulatory Toxicology Pharmacology 43:1-9.

Biography

Dr. Wendy Haines, Associate Director of Technical and Scientific Services at PharmEng Technology, has 20+ years of experience in both the research and biopharmaceutical arenas, encompassing process design, analysis, validation, project/protocol management and scientific writing. Dr. Haines is a board-certified toxicologist (DABT) and provides toxicological assessments for multi-product facilities, extractable and leachable assessments and has performed cleaning validation. Dr. Haines has been an ISPE member for 25 + years and is a Past Chair of the International YP Committee and is a Past President of the CaSA Chapter.

John VanBerschot, Senior Consultant and Lead for Cleaning Validation at PharmEng Technology, has 18+ years of experience in the pharmaceutical and biopharmaceutical industries. He has successfully implemented full Cleaning Validation programs and supported client's efforts to partially revise existing programs for Cleaning Validation; with emphasis upon regulatory compliance for both the United States and Europe. Also, he has experience with Quality Control completing analysis of manufacturing process, utility, and cleaning samples, as well as accomplishing numerous laboratory bench studies supporting Cleaning Validation such as analytical method verification and validation, swab and rinse recovery, visual residue limit, degradation, worst case residue, and relative cleanability. John has presented twice at BTEC (Biomanufacturing Training and Education Center, at North Carolina State University): "Cleaning Validation Swab Recovery Studies and Analysis: A Hands-On Workshop" and "Setting Cleaning Validation Acceptance Criteria Limits."