


# Sterility Assurance & Quality Risk Management Conference



**PDA**<sup>®</sup>  
Parenteral Drug Association  
  
Midwest Chapter



**Sterility Assurance & Quality Risk  
Management Conference**

**October  
25<sup>th</sup> & 26<sup>th</sup>**



# Cleaning Validation Risk Management

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## Brief Bio

- 36 years in Pharma and BioPharma industry
- Cleaning validation experience
- Current position and focus with Azzur Group
  - Strategy & Focused Execution
  - Seeing across CV programs



# Opening Thoughts & Content

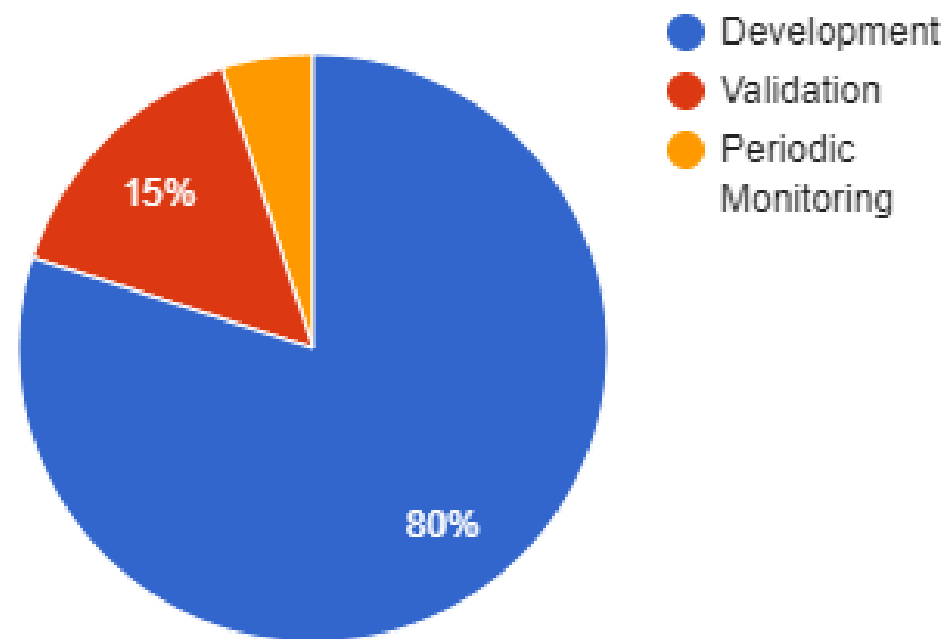
- Perceptions on Cleaning Validation
- Practical approach
- Pillars of CV program
- Risk Management synchronized with Cleaning Optimization
- Current industry explosion of Warning Letters related to CV



## Cleaning Validation Stages

- Majority of focus and efforts in development
- Let data drive decisions
- “Boring” validation

Cleaning Validation Efforts







## Cleaning Validation Foundational Pieces

- Acceptance Criteria
  - Product, cleaning agent & microbial
- Cleaning Process
  - Develop with “true owners” in mind





# Cleaning Validation Risk Management Stages

- **Risk Identification** ⇨ Residue Carryover Limits
- **Risk Analysis** ⇨ Developing & Challenging Cleaning Process
- **Risk Evaluation** ⇨ Visual and Sample Results
- **Risk Mitigation** ⇨ Optimizing and Changing Cleaning/Equipment
- **Risk Monitoring** ⇨ Periodic Monitoring of Validated Cleaning Processes



# Risk Identification – Carryover Limits

- Product, cleaning agent(s) and microbial residues
- Products can be grouped with supporting rationale/criteria
- Product Carryover-generally calculated using one of three methods:
  - 10 ppm
  - 1/1000 therapeutic dose
  - Safety based method (ADE/PDE)
- Additional requirement is equipment is visually clean.
- **Key – Impact on patients**





# Acceptance Criteria – Visual Cleanliness

- Requirement of cleaning processes

[FDA Q&A, 11/16/2022] *Equipment should be as clean as can be reasonably achieved to a residue limit that is documented to be safe, causes no product quality concerns, and leaves no visible residues.*

- Useful in development activities
- Visual Residue Limit – lowest level seen by panel of observers
  - MOC
  - Viewing angle & distance
  - Carryover limit & below



## Acceptance Criteria – Product & Cleaning Agents

- For products & cleaning agents focus on using Safety Based limits
  - Uses clinical & non-clinical data
  - Applies correction & modifying factors
- 10 ppm “default” method
- Calculate & use of “worst-case” limit





## Acceptance Criteria - Microbial

- Company specific
- Endotoxin (if sterile processing)
  - 0.25 EU/mL (WFI limit)
- Total Aerobic Microbial Counts (TAMC) and Total Yeast & Mold Count (TYMC)
- Industry standard (1 CFU/cm<sup>2</sup> to 4 CFU/cm<sup>2</sup>)
- Calculated similar to product carryover
- Absence of objectionable organisms
  - Based on route of entry



# Risk Analysis – Cleaning Development

- Have a program/procedure in place
- FDA: “at what point does a piece of equipment or system become clean?”
- Edge of failure
- Critical part of CV program-lasting labor & financial implications
- Allow time to do it right



## Risk Analysis – Cleaning Development

- Do lab studies simulating cleaning
- TACT
  - Time
  - Action
  - Chemistry
  - Temperature







# Risk Analysis – Cleaning Development

- Start simple
  - Water
  - In-house cleaning agents
- Ensure substrate compatibility with cleaning agents
- Use of coupons & spiking of product
- Use of visual checks
- Swab/rinse tests
- Identify & document critical cleaning parameters



# Risk Analysis – Cleaning Development

- Transfer lab results to manufacturing
- **Use Cleaning Verification Protocol with AC**
- Red-lined version of procedure
- Optimize cleaning and generate data
- Have cleaning team execute/manage until robust
- Training of associates



# Risk Evaluation – Visual & Swab Results

- Cleaning Verification – evaluate each event vs. carryover limits
- Target worst-case equipment locations
- Perform rinse and/or swab sampling
- Perform enhanced visual examination
- Optimize cleaning process based on data



## Risk Mitigation – Optimizing/Changing Cleaning

- Related to failing or near failing visual and sample results
- Engineering fixes
- Cleaning cycle enhancements
- More automated vs. manual cleaning
- Equipment changes
- Dedicated vs. shared equipment





# Risk Monitoring – Periodic Monitoring of Cleaning

- Starting point-Cleaning Validation
- Timing for periodic evaluation should be risk based
- Develop approved procedure
- Simplify process using forms
- Usually two-part evaluation: historical documentation & real-time sampling





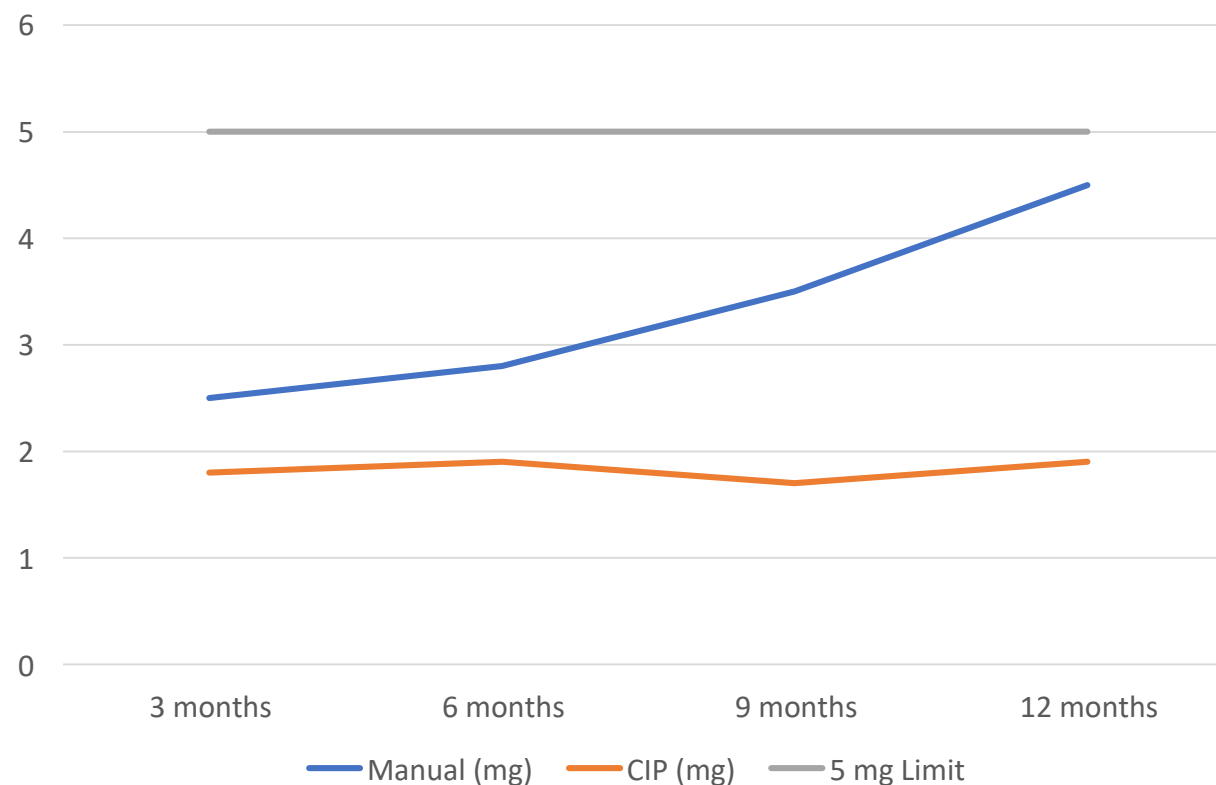
# Risk Monitoring – Periodic Monitoring of Cleaning

- Historical Documentation for equipment in timeframe:
  - Cleaning Validations/Verifications & data
  - Inline or online monitoring data
  - Manufacturing deviations
  - Change controls
  - Maintenance activities
  - Equipment logbooks
- Cleaning procedure review—validated parameters & actual process



## Risk Monitoring – Periodic Monitoring of Cleaning

- Real-time sampling:
  - Sample worst-case locations identified via validation results
  - Use current acceptance criteria limits
  - May be different equipment release criteria
- Compile and compare results
- Use results to drive decisions and future time points





# New FDA Warning Letter for Cleaning Validation

**More than 60 companies since 2020 have been hit with this observation:**

*Appropriate improvements to your cleaning validation program, with special emphasis on incorporating conditions identified as worst case in your drug manufacturing operation. This should include but not be limited to identification and evaluation of all worst-case:*

- *Drugs with higher toxicities*
- *Drugs with higher drug potencies*
- *Drugs of lower solubility in their cleaning solvents*
- *Drugs with characteristics that make them difficult to clean*
- *Swabbing locations for areas that are most difficult to clean*
- *Microbial risks related to equipment, cleaning procedures, and maximum hold times before cleaning*



# Why Incorporate Worst-Case in Cleaning

- Ensures Robust Validation
- Regulatory Compliance
- Patient Safety and Product Quality
- Provides Correct Inputs to Risk Management Process
- Industry Reputation



## Strategy for FDA Observation

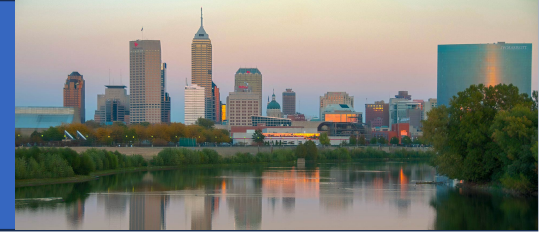
- Worst-case - highly toxic and highly potent drugs
  - Highly toxic: level of damage to organism
  - Highly potent: low concentration produces desired effect
- Review product portfolio
- Use toxicology values and therapeutic dosage
- Summarize rationale in CVMP





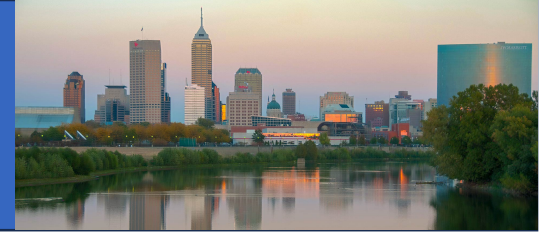
# Strategy for FDA Observation

- Worst-case – drug with lower solubility in cleaning solvents
- Most likely gap
- Lab studies probably needed
- Impact and incorporation into worst-case product
- Summarize in lab report, risk assessment and/or CVMP



# Strategy for FDA Observation

- Worst case - drugs with characteristics that make them difficult to clean
- Product formula & dosage form – dyes, excipients
- Lab studies
- Operator feedback on equipment cleaning
- Summarize in lab report and/or CVMP



# Strategy for FDA Observation

- Worst case - swabbing locations for areas that are most difficult to clean
- Review of development and CV studies
- Operator feedback on hard-to-clean locations
- Summarize swab location rationale in protocols with methodology in CVMP



# Strategy for FDA Observation

- Worst case -microbial risks related to equipment, cleaning procedures, and maximum hold times before cleaning
- Process mapping cleaning process including equipment storage
- Equipment residual moisture
- Incorporating worst-case hold times
- Profiling equipment locations for micro; past data
- Summarize in risk assessment & reference in CVMP



## Practical Tip

- Have cleaning validation program evaluated
- Best practices
- Compliance gaps
- Opportunities for improvement
- Incorporate recent changes (visual, safety-based values)
- Provide roadmap for success





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## Learn More

New White Paper:

*Elevating Cleaning Validation  
to Tackle FDA Observations*

Published October 19, 2023



Download Today!



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## Contact Information

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cleaning validation*

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# AZZUR GROUP

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