PDA Biopharmaceutical Cleaning Validation Task Force

TR29: Initiating Good Cleaning Practices

Vision, Scope and Progress

Presented at the New England PDA Meeting

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Presentation Overview

• Background Issues Driving PDA Task Force
  – TR-29 Focused Primarily on Cleaning Validation of Small Molecule Products
  – Interest in Transition from Traditional Approaches to Risk-Based Approaches to Validation
  – New Landscape for Monitoring and Validating Biopharmaceutical Cleaning Processes and Operations

• Task Force Vision and Objectives
• Proposed Document Content
• Project Schedule and Progress
Traditional Approaches To Validation

• Established, Highly Controlled Procedure
• Three Consecutive, Successful Commercial Runs
• Confidence Placed in the Consistent Performance of the Controlled Procedure Every Time
• Some Late Stage Process Development Often Occurs During Validation
• At The Time Of Commercial Manufacture Excursions/Deviations Are Evaluated and Compared to Historical Norms
Risk Based Approaches To Validation

• Focused on Process Development
  – Validation Studies Design and Execution Based Upon Risk Analysis and Management
  – Established Process Design Space Provides Identification of Critical Control Parameters and Boundary Conditions for Effective and Tight Process Controls
  – Ongoing Monitoring of Critical Control Parameters Provides Bases of Risk Review and Management With Ongoing Real Time Confirmation of Process Operation Within Validated Design Space
What is the New Landscape for Validating and Monitoring Cleaning Operations?

- Extensive Utilization of Risk Analysis and Management to Establish Focus Areas for Cleaning Validation and Ongoing Monitoring
- Development of Existing and New In-Process Material Residue Matrix from Laboratory and Pilot Scale Cleaning Data
- Generation of Product/Residue Inactivation and Fragmentation Data for Multi-Product Facilities
What is the New Landscape for Validating and Monitoring Cleaning Operations?

• Residue Limits not Based Upon MAC Calculations Unless Residues Contain Significant Levels of Active Drug Product
• Utilization of Residue Non-Specific Analytical Methods for Multi-Product Facilities
• Usage of PAT Methodologies and Data for Basis of Initial Cleaning Validation Studies and On-Going Monitoring
• Application of Statistical Process Control (SPC) Methodologies for Assessing Drift and Defining Re-Validation Requirements
Vision and Objectives of New Technical Report

- Convene Subject Matter Experts in Cleaning Validation from Industry and Regulatory Communities
- Provide the Industry with Practical, Experience-Based Methodologies for the Implementation of Cleaning Validation Current Best Practices
Scope of Document

- Regulatory Aspects of Cleaning Validation
- Master Planning for Cleaning Validation
- Risk Assessment and Management
- Cleaning Process Design Space
- Sampling and Analytical Methods
- Acceptance Limits
- Maintenance of Validated State of the Cleaning Process
- Auditing the Cleaning Process
- Process Analytical Technology and Rapid Analytical Tools for Cleaning Process Monitoring and Control
- Special Considerations for Cleaning Validation
Regulatory Aspects of Cleaning Validation

• Discuss and Review Regulations Relevant to the Validation Of Cleaning Operations
  – CFR part 211 and CFR part 600
  – EMEA Annex 15

• Provide Introduction and Glossary of Relevant Regulatory Standards and Technical Publications

• Summary of Significant Points in Each Regulation
Regulatory Aspects of Cleaning Validation

• Propose Resolution of Conflicting Regulatory Requirements Where Applicable
• Present Table (Diagram) Of Validation/Submission Requirements for Cleaning Validation at Various Clinical/Production Stages
• Discuss Role of Risk Assessment in Validation Approach
• Present Table Of Actual Regulatory Submission Content, Approach To Development Of Content And Language
Master Planning for Cleaning Validation

• Review Merits of Comprehensive and Prospective Master Planning
  – Strategic and Tactical Considerations

• Evaluate Regulatory Agencies Increasing Focus Quality Systems
  – Role of Validation Master Plans in GMP and PAI Inspections

• Detailed Cleaning Validation Master Plan Outline Presented as an Example

• Practical Examples and Case Studies Presented to Illustrate Key Points
Risk Assessment and Management

• Review and Evaluation of Risk-based Approaches to Cleaning Validation Studies
• Review of ICH Q9 Content with Respect to Cleaning Validation
• Practical Cleaning Validation Risk Analyses and Management Tools
• Recent FDA Comments and Observations on Risk-Based Validation
• Value of Cleaning Process Design Space in Risk Assessment and Control
• Evaluation Of The Role Of PAT In Risk-based Cleaning Validation Studies
• Present Case Studies From Manufacturing Facilities to Illustrate Risk-based Cleaning Validation Principles and Practices
Cleaning Process Design Space

- Understanding Cleaning Parameters that are Important to the Efficacy of Cleaning Processes
- Design Space Data Crucial for the Development of Robust Cleaning Processes (ref. ICH Q8)
- Characterization of Critical Control Parameters and Their Boundaries (Edges Of Failure)
  - Basis For The Definition The Design Space Around Cleaning Processes for all System Residues (product, rouge, cleaning agents, material compatibility, etc.)
  - Practical Methodologies of Experimental Design (DOE) for Cleaning Experimentation,
  - Coupons, Pilot Scale Process Development Equipment, etc.
- Importance of Design Space Understanding for Effective Control and Ongoing Monitoring
Sampling and Analytical Methods

• Review Criteria for Effective Selection of Sampling and Analytical Methods
  – Consider Residue Characterization, Sensitivity, Accuracy, Precision And Robustness
  – Role of Product Residue Fragmentation by Cleaning Solutions
• Selection Strategies for Sampling and Analytical Methods Based Upon Their Traceability to Anticipated Residues
• Multi-Product Facility Issues
  – Product-To-Product Cleaning Requirements as Related to Sampling and Analytical Methods Selection
• Bases for Residue Specific or Residue Non-Specific Analyses Selected for Characterization Of Cleanliness
• Visual inspection still required
• Utilization Of Contract Laboratories For Sample Analysis Will Be Reviewed.
Acceptance Limits

• Establishment of Scientifically Based Acceptance Limits for Biopharmaceutical Manufacturing Facilities
• Issues Related to Lack of Active Drug Product in Significant Levels for Many Biopharmaceutical Unit Operations
  – Dosage Carryover-Based Limits may be Inappropriate
• Establishment of Acceptance Limits Based Upon Criteria Other than Dosage Carry-Over
  – Cleaning System Performance, Product Residue Fragmentation and Analytical Method Limit Of Quantification and Supporting Science-Based Logic
  – Visual Detection Limits
• Practical Application of Principles Illustrated Through Case Study Example
Maintenance of Validated State of the Cleaning Process


• Ongoing Real-Time Data Analysis for Detection of Cleaning Process Drift
  – Event-based Versus Time-Based Requalification

• On-going Visual Inspection Results Monitoring

• Present Case Studies From Manufacturing Facilities to Illustrate Current Best Practices for Maintenance of Validated State of Cleaning Processes
Auditing the Cleaning Process

- Review of Scientific Bases for Critical Aspects of Cleaning Validation Program
  - Residue Characterization, Sampling and Analytical Methods, Acceptance Limits for Lot-To-Lot and Product-To-Product Cleaning, Worst Case Residues, Samples Locations, Logic Behind Grouping Strategies, and Clean and Dirty Hold Times
- Auditing of Producers of “Out-Sourced” Materials
- Auditing Executed Protocols
  - Deviation Resolution and Re-Execution
  - Change Management
  - Legacy Systems
- Ongoing Evaluation of Cleaning Operations
  - Assessment of “Drift” and Requalification Requirements (PAT)
Process Analytical Technology and Rapid Analytical Tools for Cleaning Process Monitoring and Control

• Effective Control and Monitoring Using Process Analytical Technologies (PAT) Methodologies and/or Rapid Analytical Tools Combined With Comprehensive Understanding Of Cleaning Process Design Space
• More Effective Control And Monitoring Of Cleaning Process Parameters Within Narrowly Defined Ranges
• Ensure High Probability of Cleaning Effectiveness in Real Time
• Validation Based Upon Real Time Data Collection and Analysis Rather Than “Three Consecutive Commercial Scale Run” Methodology
• Practical Approaches for Implementation of PAT for Cleaning Processes Including Case Study
## Special Considerations for Cleaning Validation

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Project Schedule and Progress

• Outlines Completed for Many Sections
• Section Drafts Completed for Four Sections
• Task Force to Complete and Edit Draft Sections Through Q4 2008
• Entire Draft Document to be Available for General Review and Comment During Q1 2009
• Final Document to be Submitted for Publication Q3 2009
Questions, Comments, Suggestions?

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