# PDA Biopharmaceutical Cleaning Validation Task Force

***TR29: Initiating Good Cleaning Practices***

## *Vision, Scope and Progress*

Presented at the New England PDA Meeting

November 12, 2008


**-Prepared By -**

**John Hyde, Chairman and Founder**

**Presented by:**

**Richard Jushchyshyn, Principal**

**Hyde Engineering + Consulting, Inc.**


Hyde
Engineering + Consulting

# 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
- Document Current Principles and Practices for the Validation of Cleaning Processes for Biopharmaceutical Manufacturing Equipment Systems
- 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
  - FDA *Guide to Inspections Validation of Cleaning Processes* (1993)
  - Health Canada *Cleaning Validation Guidances* (2000)
  - 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

- Review of Strategies and Practices Using Rigorous Ongoing Monitoring and Control for Assurance of Effective Cleaning Process Operation
- 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 Sate 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

| | |
|---|---|
| **Parts washers/ COP washers** | **TFF** |
| **Cart washer** | **Filter housings** |
| **Glass washers** | **Ultrasonic cleaning** |
| **Manual cleaning** | **Homogenizers** |
| **Tanks** | **Centrifuges** |
| **Lines** | **Product contacting vs. Buffer/media** |
| **Chromatography** | **Stopper & Vial Washers** |

# 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?

Please contact:

John Hyde

John.Hyde@Hyde-EC.com

303-641-5468

Hyde
Engineering + Consulting