# Introduction
# Building Quality during Manufacture

Rajesh K. Gupta, Ph.D.

Biologics Quality & Regulatory Consultants, LLC

*Analyze, Strategize & Operate – Different & Smart*

rgupta@bqrc.org

1 240 246 0126

DCVMN Training Workshop – Hyderabad, India
April 4 – 8, 2016

## Outline of Presentation

- Some Definitions
- Quality Paradigm of Biological Products
  - Shift from "Final Testing" on Product to "Build Quality" in the Product during Manufacture
- How to Build Quality in the Product?
  - Good Manufacturing Practices (GMP)
  - Quality by Design (QbD)
  - Process Analytical Technologies (PAT)
- Quality Metrics (Draft FDA Guidance)
- What do you get by Building Quality in Product?
- Data of Compliance vs Data of Exception

# Definitions

- Attribute: A Quality or Feature – as a Characteristic or Inherent Part of something or someone
- Critical Quality Attribute (CQA) – A Physical, Chemical, Biological, or Microbiological Property or Characteristic that should be within an Appropriate Limit, Range, or Distribution to ensure the Desired Product Quality
- Out-of-Specification (OOS) Result – Test Results that are Outside the Specifications or Acceptance Criteria established in Drug Applications, Drug Master File, Official Compendia, or by the Manufacturer
- Invalidated OOS – An Out-of-Specification Result that was Invalidated



# Definitions (Contd.)

- Parameter: Range, Limits or Boundaries that Set the Conditions of Operation
- Critical Process Parameter (CPP): A Process Parameter whose Variability Impacts a CQA and Therefore should be Monitored or Controlled to Ensure the Process produces the Desired Quality
- Design Space: Multidimensional Combination & Interaction of Input Variables (Material Attributes) & Process Parameters that provide Assurance of Quality
- Quality Target Product Profile (QTPP): A Prospective Summary of Quality characteristics of DP that ideally will be achieved to ensure the Desired Quality, taking into account safety and efficacy of the drug product

# Conventional Quality Paradigm

## Quality by Testing Representative Samples

- Historically, Biological Products, mainly Vaccines & Antitoxins were Made in Flexible Manufacturing Environment with Rigorous Testing
  - Empirical Development
  - Manufacturing Process Based on Retrospective Data
- Focus on Testing to Document Quality
  - Product Release based on Batch Data
  - Intermediate Products (**Process is the Product**)
  - Final Products (Animal Tests for Safety and Potency)
- Regulations Based on Testing Final Product
  - 21 CFR 610 General Biological Product Standards
  - Pharmacopoeia Monographs (USP, EP, JP, etc.)



# Shift in Quality Paradigm

## Quality by Consistency in Manufacture & Testing

- Good Manufacturing Practices (GMP) Regulations Started Shift in Quality Paradigm
  - Quality Systems Concept
  - Documentation
  - Investigations
  - Prospective Validations (Facilities, Process, Utilities, Methods, Cleaning, etc,)
  - Monitoring of Facilities, Environment, Utilities, Processes, etc
  - Components, Intermediates and Final Product Testing
- Deletion of Product Specific Requirements (US)
  - 21 CFR 620 (Bacterial Vaccine) & 21 CFR 630 (Viral Vaccines)

# New Quality Paradigm

## Build Quality in the Product

- Quality cannot be Tested; should be Built in by Design
- Quality by Design of Effective and Efficient Manufacturing Processes
- Use of Scientific and Quality Risk Management Principles and Quality Control Strategies based on understanding & Knowledge of Product and Process
- Identify Critical Starting & Raw Materials and Process Parameters (CPP) Affecting Quality
  - Evaluate and Determine, if possible, their Relationship with Critical Quality Attributes (CQA)
- Design a Process with On-line or At-line Monitoring of CPPs and CQAs



# FDA Guidance: Process Validation – General Principles and Practices, January 2011

## "Drug Fit for its Intended Use"

- Quality, Safety & Efficacy is Designed or Built into Product
- Quality cannot be adequately Assured merely by In-process and Finished-Product Inspection or Testing
- Each Step of a Manufacturing Process Controlled to Assure that Finished Product Meets all Quality Attributes including Specifications

cGMP Requires that Manufacturing Processes be Designed & Controlled to assure that In-process Materials & Finished Product meet Pre-determined Quality Requirements -Consistently and Reliably

## FDA Guidance: Process Validation – General Principles and Practices, January 2011

Homogeneity within a Batch & Consistency between Batches - Goals of Process Validation Activities

- Attribute(s)
  - Quality, Product, Component
- Parameter(s)
  - Process, Operating & Equipment
- All Attributes & Parameters should be Evaluated for their Roles in the Process & Impact on the Product or In-process Material
- Re-evaluated as New Information is Available
- Degree of Control over Attributes or Parameters should be as per their Risk to Process and Process Output



## FDA Guidance: Process Validation – General Principles and Practices, January 2011

- Controls to include both Examination of Material Quality & Equipment Monitoring
- Special Attention to Control Process through Operational Limits and In-process Monitoring Essential in 2 Possible Scenarios:
  - When Product Attribute not readily Measurable due to Limitations of Sampling or Detectability (e.g., Viral Clearance or Microbial Contamination) or
  - When Intermediates & Products cannot be highly Characterized and well-defined Quality Attributes cannot be Identified

## FDA Draft Guidance: Quality Metrics
July 2015 (Currently Not Applicable to Vaccines)

Vision for 21st Century Drug Manufacturing

"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."

- Promotes Responsible Practices & Quality driven Corporate Culture
- Identify Situations for a risk for Drug Supply Disruption
- Improve FDA's Evaluation of Drug Manufacturing & Control Operations



## FDA Draft Guidance: Quality Metrics, July 2015

What are Quality Metrics?

- An objective measure of the quality of a product or process
- An objective measure of the quality of a site
- An objective measure of the effectiveness of systems associated with the manufacture of pharmaceutical products, including the pharmaceutical quality system
- Required under CGMPs Annual Product Review Manufacturing data, SPC charts, process capability output

# FDA Draft Guidance: Quality Metrics

July 2015

## Potential Quality Metrics?

- Lot Acceptance Rate or Batch Failure Rate
- Product Quality Complaint Rate
- Invalidated Out-of-Specification (OOS) Rate
- APRs or PQRs on Time Rate (within 30 Days of due Date)

## Optional Quality Metrics

- Senior Management Engagement
- CAPA Effectiveness
- Process Capability/Performance (Statistical Process Control)

## Future

- Robust QM Program requires Continual Improvement
- Metrics Specific to Product, Site & Supply Chain



# Building Quality in a Biological Product

## Challenges in Building Quality for Biologics

- Requirement for Sterility of Biologics in Design and Control of the Manufacturing Processes
- Understanding and Managing Inherent Variability in Manufacture
  - Starting and Raw Materials of Biological Origin
  - Complex Biological Processes
  - Unstable and Microbial Growth Supporting Intermediates
  - Bioassays with large Inherent Variability

## Recommendations

- Focus on Science and Understanding of Product, Process & Variability
- Understand Process and Product to Identify and Manage Sources of Variability

## Assuring Microbiological Quality of Biologics

- Microbiological Methods & Testing Do NOT Provide Complete or Absolute Absence of Viable Organisms
  - Robust Microbiology Programs Provide Assurance of Microbiological Quality

How to Assure Microbiological Quality?

- Testing, Validation, Monitoring & Verification
  - Aseptic Processing & Environmental Monitoring
- Terminal Sterilization
  - Biological Products Generally Not Terminally Sterilized
- Microbial Removal/Reduction/Inactivation
  - Validation of Manufacturing Process

**Build Microbiological Quality into a Product**



## Quality by Design (QbD)

- A Systematic Approach to Development, Starting with Predefined Objectives
- Science and Risk Based Assurance of Quality
- Emphasis on Understanding Product and Process & Process Control based on Sound Science and Quality Risk Management
- Determine Design Space
- Design Process with Online Monitoring & ability to Adjust CPPs (within Design Space) by Measurement of CQAs
- Continuous “Real Time” Quality Assurance

# FDA's View on QbD

(Riley & Li, AAPS Pharma Sci Tech 2011, 12:114-118)

- Product/Process Design & Development
  - Define Desired Product Performance
  - Identify Product CQA
  - Design Process and Formulation to meet Product CQAs
- Risk Assessment & Risk Control
  - Understand Impact of Material Attributes and Process Parameters on Product CQAs
  - Identify & Manage/Control Sources of Variability in Materials & Process
  - Continually Monitor and Update Process to Assure Consistent Quality



# Process Analytical Technologies (PAT)

- Tool or System to Design, Analyze, and Control Process to Implement QbD
  - To Understand Scientific & Engineering Principles
  - To Identify Variables affecting Quality
  - To Monitor and Control Process (in Real Time) with Feed-Forward and Feed-Back Controls
  - To Facilitate Tracking & Trending of Process Operations to Support Continuous Improvement Changes
- FDA started PAT discussion publicly in 2001 with FDA's PAT Guidance in 2004
- Pharmaceutical Quality for the 21st Century Initiative included both fundamental concepts of QbD and PAT

## Benefits of New Quality Paradigm (QbD)

- Robust Process based on Science with Flexibility to Make Changes within Design Space without Regulatory Notifications/Approvals
- Allows Continuous Improvement for Enhanced Compliance and Efficiency, and a Better Product
- Upstream Quality Control with Possibility of Real-Time Release or Reduced End-Product Testing
  - Reduction in Cycle Times
  - Reduction in Product Reject & Waste
- Provides a higher level of Assurance of Product Quality
- Flexible Regulatory Policies to Accommodate New Scientific Knowledge and Modern Technologies
  - Increased Use of Automation and New Methods



## Monitoring & Managing Process

- Historically, Manufacturing Processes for Biologicals have been Monitored

  "Process is the Product" Philosophy
  - Surrogate Markers (pH, $DO_2$, metabolites Levels, etc. during fermentation) to Ensure Expected Process – Indicator of Purity
  - Microscopic Examination (Gram's Staining) – Indicator of Purity
  - Immunochemical Methods (Flocculation Test [Lf, Kf], Agglutination, ELISA, etc.) – Indicator of Yield
  - Intermediate Products (Toxins for Lethality)
- Action Taken to Terminate or Continue Process

## Role of Analytical Methods in QbD

- Scientifically Sound & Reliable (Specific, Accurate & Precise) Methods – Critical for
  - Drug Development
  - Manufacture by Conventional Paradigm (Quality by Testing)
  - Manufacture by New Paradigm (QbD)
- Analytical Methods in QbD
  - Identifying Starting/Raw Materials & CPP affecting Quality
  - Identifying CQAs
  - Designing Process and Defining Design Space
  - Implementing PATs
    - Analytical Methods, Probes, Chips, etc.



## Analytical Methods for PAT & QbD

- New and Modern Methods
  - Technological Development in Analytical Sciences and Instruments
    - Powerful Tools to Characterize Biologicals
  - Developments in Proteomics and Genomics
    - Highly Sensitive, Precise and Accurate Methods to Characterize Biologicals and to Assess Purity of Biologicals
- Concept of Well Characterized Biologicals
  - Implemented Modern Analytical Methods
  - Not Applicable to Complex Biological Products, Vaccines at DP

## Reliability of Methods for QbD

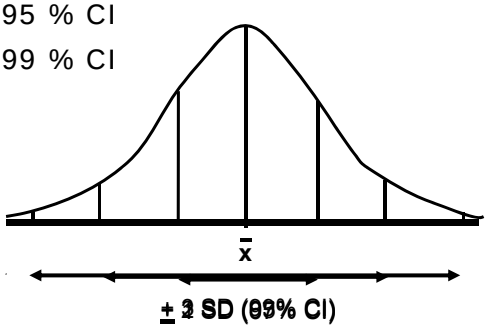
- At Least as Reliable as Characterization Tests
  - Tests used Extensively during Development to Understand Product (Structure, Purity) and Mechanisms of Action (Proof of Concept)
  - Scientifically Sound, with Robust Method Design
  - Usually Not Validated, Varying Degree of Qualification (Suitable for Intended Purpose)
  - Usually Not Part of Release Tests
  - Used in Support of Process or Other Changes to Approved Applications
- Probes or Chips
  - Appropriately Validated and Periodically Calibrated and/or Verified



## Analytical Methods
## Suitable for Intended Purpose
## Important during Root-Cause Analysis

# Normal Distribution

- Data Must be Normally Distributed for Relying on
  - Mean
  - Standard Deviation (SD)
  - Coefficient of Variation (CV) or Relative SD (RSD)
- ± 1 SD = 67% Confidence Intervals (CI)
- ± 2 SD = 95 % CI
- ± 3 SD = 99 % CI







# Understanding Inherent Variability of a Method

- SD Depends upon Numbers
- CV or % RSD Normalizes Data
- Understanding CV
  - 10% CV or RSD =
    - ± 20% Variability at 95% CI
    - ± 30% Variability at 99% CI
- If Data Not Normally Distributed, SD, CI, Not very Useful
  - Use Non-Parametric Statistics

## Design of Analytical Method for "Intended Purpose"

- Method for Release to Support Specifications (80 – 120%), Method Validated with a 25% CV
  - Not Suitable for Intended Purpose
    - At 95% CI, this Method can Support 50 – 150% Specifications
- Managing Variability
  - Understanding Source of Variability
  - Random Variability – Mean of Multiple Determinations
- Method Validation Parameters (Precision & Accuracy) Based on "Intended Use", NOT on the Capability of the Method



## Data, Observations & Results

Analysis or Monitoring of Data, Observations & Results for Compliance with Standards/Specifications

- Data of Compliance
  - Meeting Standards/Specifications
  - Used to Release Product
  - Trending, Tracking, Periodic Review
- Data of Exception
  - Not Meeting Standards/Specifications
  - Includes Deviations, Non-Conformances, Out of Specifications (OOS) Results, Invalid Results
  - Needs Immediate Attention/Notification & Investigation

## Control Limits

- Acceptable Operating Limits
  - Range of Values for Routine Operation (Validated) or Acceptable Attributes or Parameters
  - Generates Product of Consistent & Desired Quality
  - Generates Product "Suitable for Intended Use"
- Alert Limits
  - Range of Values, when Exceeded are Potential Drift from Acceptable Operating Limits
  - Warning Signal for Potential Problems
  - Frequent Monitoring may be Required
- Action Limits
  - Range of Values, when Exceeded are Apparent Drift from Acceptable Operating Limits
  - Pre-Determined Action Required, including Investigation
- Specifications
  - Range of Values, when Exceeded Process, Product, Equipment, Environment & Utilities – Unacceptable for Use



## Summary and Conclusions

- New Paradigm of Building Quality in the Product rather than Testing of Representative Samples
- Regulatory Agencies Support and Encourage Use of Quality by Design Approach
- Design Manufacturing Process based on Sound Scientific Principles and Quality Risk Management Approach
- Analytical Methods Play a Central Role in Assuring Quality of the Product
- Analysis of Observations, Data & Results for Compliance or Exception


Thank You!
Biologics Drugs
Analyze, Strategize & Operate
BQRC
Different & Smart
Quality Regulatory Compliance