

Critical Quality Attributes, Critical Process Parameters, Tracking and Trending

Rajesh K. Gupta, Ph.D.

Biologics Quality & Regulatory Consultants, LLC

Analyze, Strategize & Operate – Different & Smart

rgupta@bqrc.org

1 240 246 0126

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Outline of Presentation

- Critical Quality Attributes
 - Relation to Quality
 - Identifying CQAs
 - Examples
 - Key Performance Attributes
- Critical Process Parameters
 - Key Process Parameters
 - Identification and Evaluation
- Trending and Tracking
 - Selection of Attributes and Parameters
 - Periodic Reviews
 - Actions



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
 - Identity, Strength (Potency), Purity, Safety
- A Link to Clinical Safety & Efficacy
 - Potency as Surrogate Marker for Efficacy
 - Specific Toxicity – Markers of Residual Toxin or Reversion of Toxin, Surrogate for Safety
 - Purity – Surrogate for Safety and Marker for Consistency in Manufacture
- CQAs – Key Elements in Product Development

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Defining or Identifying CQA

- Due to Complexity of Vaccines, Defining or Identifying CQAs is Difficult
 - Many Attributes are Explored during Development, starting with all Product Attributes that could be Characterized
- Prior Knowledge & Current Data (Pre-Clinical, Clinical) on the Structure-Function Relationship or Mode of Action
 - Antigenicity of Potential Protective Epitopes
 - Amount of Conjugate or Limit of Free Saccharide for Conjugate Vaccines
 - Number of Microbial Particles for Live Vaccines
 - Correlation of Animal Protective Studies to Structure, Antigenicity or Other Attributes
- A Risk-Assessment Tool to Define CQAs

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Severity Analysis to Identify CQAs

- Impact Score – Level of Impact on Safety and Efficacy
- Uncertainty Score – Level of Uncertainty in Prediction of Impact

$$\text{Severity} = \text{Impact} \times \text{Uncertainty}$$

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Example, Impact Scores

From: A-VAX: Applying Quality by Design to Vaccines,
CMC-Vaccines Working Group, May 2012

Impact Score	Efficacy	Safety and Tolerability (Adverse Events, AEs)
Very High 25	Significant Change	Severe AE prevents normal, everyday activities (e.g., prevent attendance at school/kindergarten/day-care center, requiring medical attention or advice). Significant increase in severity and/or frequency.
Moderate 8	Moderate Change	Moderate Sufficiently discomforting to interfere with normal everyday activities. Moderate but detectable increase severity and/or frequency over placebo.
Minimal 2	Minor to No Change	Mild Easily tolerated, causing minimal discomfort and not interfering with everyday activities. Similar to placebo.

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Example, Uncertainty Scores

From: A-VAX: Applying Quality by Design to Vaccines,
CMC-Vaccines Working Group, May 2012

Score	Uncertainty
Very High 5	No information available
High 4	<i>External</i> information available from literature on related vaccine(s)
Moderate 3	Data from <i>internal</i> laboratory or nonclinical studies with this antigen:adjuvant complex, or <i>internal</i> data extrapolated from related vaccine(s)
Low 2	Supportive data from <i>clinical studies</i> with this antigen:adjuvant complex
Minimal 1	Published limits widely accepted by regulatory and scientific community

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Example, Severity Scores

From: A-VAX: Applying Quality by Design to Vaccines,
CMC-Vaccines Working Group, May 2012

		Uncertainty Score					
		1	2	3	4	5	
Impact Score	2	2	4	6	8	10	} Severity Score
	8	8	16	24	32	40	
	25	25	50	75	100	125	

Critical ≥ 25 , Red; Borderline $>10 - 24$, Yellow; Less Critical ≤ 10 , Green

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Progression of Quality Attributes

- Potential CQAs get defined as True CQAs later in Development
- All CQAs are not Release Specifications
- Advances in Analytical Methodology and Implementation of Modern Methods will Improve Understanding and Role of CQAs in Assuring Product Quality
- CQA Impacting Safety & Efficacy over Shelf Life (Stability)
 - Residual Moisture – No immediate Impact on Safety & Efficacy, but High Moisture Impacts Potency over Time
- Life Cycle Approach for Vaccine Control Strategy

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Performance Attributes

- A Physical, Chemical, Biological, or Microbiological Property or Characteristic whose Variability might have a Potential Impact on Process Performance (Yield, Time, Cost of Goods, etc)
- Key Performance Attribute (KPA) – When Controlled Ensures Optimal Process Performance
 - pH, Osmolality, Inoculum
- Ensure Adequate Product Supply
- May be Included in Control Strategy to Meet Business Goals

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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
 - Criticality of a Process Parameter Linked to Defined Acceptable Range of that Parameter
- Key Process Parameter (KPP) when Maintained in a Narrow Range Ensures Consistent Process Performance
 - KPPs Not affect Product CQAs, but Ensure Optimal Process Performance
- CPP and KPP Identified through Risk Analysis followed by Univariate or Multivariate Experiments

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Identification & Evaluation of CPPs

- As with CQAs, Scientific Understanding & Historical Information Initially used to Identify CPPs & KPPs
 - Factor Risks Documented through Cause & Effect Analysis
 - Evaluated in Multifactor Design of Experiments (DOE) or "One Factor at a Time (OFAT)" Experiments
 - Data Evaluation by Statistical Analysis (ANOVA) and Plots (Pareto Chart, Half Normal Plot)
- CPP and KPP Identified through Risk Analysis followed by Univariate or Multivariate Experiments
- Continuous Process Verification during Commercial Manufacture also Identifies CPPs & KPPs
- Mathematical Modeling to forecast Probability of OOS

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Manufacturing Control Strategy

- Input Materials Control (Critical Raw Materials)
- Process Controls
 - Procedural Controls
 - Process Parameter Controls
 - PAT
- Test Controls
 - In-process Testing
 - Release Testing (Specification)
 - Characterization or Comparability Testing
 - Process Monitoring
- Continuous Process Verification

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Continuous Process Verification

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

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

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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

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Trending/Tracking

- Part of Process Verification & Monitoring
- Metrics on Manufacturing Operations (Including Laboratory) for
 - First Time Right
 - Compliance Rate
 - Warning for Potential Problems
 - Re-defining CQAs, CPPs, Limits, Specifications, etc.
 - Part of Continual Improvement
 - Needs for Training
 - Sustainable Compliance
 - Valuable Information for Management Review

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Data for Trending/Tracking (Examples)

- Appropriate CQAs, KPAs, CPPs, KPPs, etc.
- Metrics on Equipment Performance
- Metrics on Utilities
- Laboratory Metrics
 - Known Laboratory Errors
 - Invalid Tests
 - OOS
 - Invalidated OOS
 - Any Other Metrics
 - Equipment Performance, Calibration, etc.
 - Critical Reagent Performance

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Methods System Suitability Examples

- Standard Curve Parameters
 - Linear – r, Slope, Intercept, 50% End Point
 - 4 – Parametric, Upper & Lower Asymptotes, r, slope, 50% End Point
- Background
- Internal Controls
 - Limits Sets at 95 or 99% CI, Parallelism (Slope Ratio)
- Chromatographic Procedures
 - CV of Injection Repeatability
 - Performance of Standards/Controls
 - S / N for Quantitative Impurities and Limits Tests
- Non-chromatographic procedures
 - Titration - Blank
 - Polarimetry - Rotation Standards

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Procedure – Tracking/Trending

- Written SOPs with Pre-defined
 - Metrics, Data, Parameters, Attributes
 - Frequency of Evaluation
 - Evaluation Methods (Statistical Analysis)
 - ❑ Statistical Process Control Softwares,
 - ❑ Trends
 - ❑ Data of Exception (Exceeding Alert or Action Limits)
 - Actions to be Taken (CAPA)



Summary and Conclusions

- Understanding Critical Quality Attributes (CQAs) and their Role in Quality of Drugs is Critical
- Critical Process Parameters (CPP) need to be Identified and Controlled to assure Quality of Drugs
- A Manufacturing Control Strategy is developed based on CQAs and CPPs
- Various Attributes, Parameters and Other Metrics need to be tracked and Monitored for Continuous Process Verification
- These are all Important Tools for Building Quality during Manufacture of Drugs



