Critical Quality Attributes, Critical Process Parameters, Tracking and Trending

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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

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

Severity Analysis to Identify CQAs

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

Severity = Impact X Uncertainty

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.

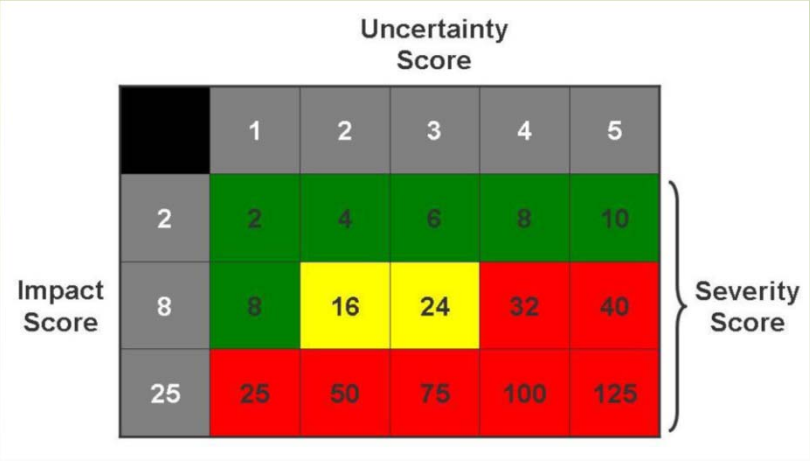
Example, Uncertainty Scores

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	*External* information available from literature on related vaccine(s)
Moderate 3	Data from *internal* laboratory or nonclinical studies with this antigen:adjuvant complex, or *internal* data extrapolated from related vaccine(s)
Low 2	Supportive data from *clinical studies* with this antigen:adjuvant complex
Minimal 1	Published limits widely accepted by regulatory and scientific community

Example, Severity Scores

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



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

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

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

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

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

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

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

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

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

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

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

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 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


Thank You!
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