Current Best Practices in the Definition of Process Parameters for Development of Control Strategies

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CMC Strategy Forum Europe
Outline

• Background – Nomenclature
  ▪ PDA TR 42
  ▪ A-Mab

• Evolution of Industry

• Regulatory Feedback

• Best Practices
PDA TR 42

• Published in 2005
• Separates variables / conditions into two categories
  - Operational Parameters (aka Process Parameters, inputs)
  - Performance Parameters (aka Performance Attributes, outputs)
  - Further segregated based upon impact to product critical quality attributes

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Essentially, parameters were lumped into three classifications

- **Critical**
  - Operation outside a narrow range affects a CQA

- **Key**
  - Operation outside a narrow range affects performance

- **Non-key**
  - Parameters that have wide operating ranges
  - Doesn’t differentiate as to what the parameter affects
A-Mab Case Study

- Published in 2009
- Uses similar terminology to TR 42
- If parameter affects quality attribute then critical
  - Either CPP or WC-CPP
- Introduced idea of in-process quality attribute
  - Part of batch release
  - Parameters that affect classified as critical
- If parameter affects process performance then key
  - Defined general process parameter (GPP) as anything that is not critical and is well controlled, ie, all other parameters
- Defined key performance attribute as in-process output that measures process performance, eg yield
## A-Mab Case Study

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Industry evolution

• In general, A-Mab describes a way to develop a risk-based control strategy and the definitions for a clear, uniform “language”

• Unfortunately, scientist cannot leave well enough alone…
  ▪ Parallel evolution of definitions/strategy from many companies
  ▪ Opinion that “we can improve the A-Mab language”

• Many companies modified definitions and terminology for control strategies
  ▪ Simplified translation to manufacturing documents
  ▪ Reduce number of levels or tiers

• Differences between quality-related and process-related became less clear
Industry evolution

• The term “key” became the second tier of parameter classification
  1. Critical
  2. Key
  3. Non-critical, non-key

• Key variables expanded in coverage to include:
  ▪ critical, but easily controlled
  ▪ variables affecting process performance with narrow ranges
  ▪ Tier 3 was everything else

• This simple three-tiered system was a natural evolution of the control strategy
  ▪ Companies would only put tiers 1 and 2 variables in the filings.
As a result of this pilot program, the EMA and FDA reached agreements on a wide range of QbD aspects as reflected in the Q&A below.

3. Question: Would the Agencies accept a three-tier classification of criticality for process parameters?

Answer… The Agencies do not support the use of the term Key Process Parameters (KPP) since it is not an ICH terminology. Furthermore, experience reveals that different applicants use the term “key” differently, leading to more difficult internal communication. The fact that a risk of failure is mitigated by applying a robust proactive control strategy should not allow for the underestimation of assigning criticality.
Where to go from here?

- Evolved nomenclature not aligned with current regulatory guidance

- Use A-Mab?
  - Still uses the “key” designation even though specifically not for Quality Attributes

- TR 42 not sufficient

- Develop / evolve the terminology further?
IPC Nomenclature Best Practices

• What are the needs?
  ▪ Patient safety
  ▪ Link to QAs/CQAs separate from process performance
  ▪ Regulatory Transparency
  ▪ Translatable to MBRs
  ▪ Relatively Simple

• What references should be considered?
  ▪ ICH guidelines (Q8-Q11)
  ▪ FDA guidance on process validation (2011)
  ▪ EMA guideline on process validation (2014)
  ▪ EMA-FDA Lessons Learnt (2013)
  ▪ Etc.
IPC Nomenclature Best Practices

• What would be considered “best practice”?
  - Should include both inputs and outputs
  - Should be clearly delineated
  - Needs to be multi-tiered
    - All process variables are not created equal
    - Separate designation for variables that affect quality and performance.
  - No nested ranges
  - Variables that affect a CQA are critical
  - Not contain “key”
  - Easy to follow (decision tree)
  - Be defendable
IPC Nomenclature Best Practices

- Should include inputs and outputs
  - Input = process parameter
    - Independent variable, can be changed, modified, and/or controlled by human/machine interaction or intervention
    - Ex: bioreactor temperature, buffer pH, protein load, flowrate
  - Output = performance attribute
    - Dependent variable, is a direct outcome of the process
    - Ex: bioreactor titer, step yield, bioburden
IPC Nomenclature Best Practices

- Needs to be multi-tiered
  - Tier 1 = critical
  - Tier 2 = action
  - Tier 3 = alert
  - Tier 4 = monitor

- Why do we need so many levels?
  - Debatable what is the “correct” number
  - Striving for best practices – include flexibility in control strategy
IPC Nomenclature Best Practices

- Critical process parameter, critical performance attribute
  - Affect CQA, QA
  - Designated acceptable ranges
  - If outside acceptable range, lot rejection

- Process parameters, performance attributes
  - Affect process performance
  - Can be Tier 2 = action or Tier 3 = alert
  - Deviations from action ranges result in an investigation that may lead to lot rejection, CAPA, etc.
  - Deviations from alert ranges may result in an investigation, ex, a deviation in 2 out of 5 lots results in an investigation

- Monitored parameters, monitored attributes
  - Parameters/attributes without defined ranges
  - Data trended as an early warning for process drift
  - Statistical Process Control
## Review of Past Nomenclature

### TR 42

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### A-Mab

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## IPC Nomenclature Best Practices

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<td>PP, MP</td>
<td>PA, MA</td>
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IPC Nomenclature Best Practices
## IPC Nomenclature Best Practices – Protein A

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<thead>
<tr>
<th>Process Variable</th>
<th>Description</th>
<th>Range Classification</th>
</tr>
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<tbody>
<tr>
<td>Column characteristics (bed height/HETP/As)</td>
<td>Data shows wide range of acceptable values, separation relatively insensitive to bed height and HETP</td>
<td>Alert (PP)</td>
</tr>
<tr>
<td>Equilibration / Wash 1</td>
<td>Data shows buffer pH, conductivity, and volume have little effect on step performance</td>
<td>Alert (PP)</td>
</tr>
<tr>
<td>Protein Load</td>
<td>Overloading results in yield loss but no increase in pool impurity levels</td>
<td>Action (PP)</td>
</tr>
<tr>
<td>Wash 2 buffer pH</td>
<td>Optimal performance is within a narrow pH, adequate performance is over a wider pH range. Large effect downstream on subsequent step</td>
<td>Acceptable (CPP)</td>
</tr>
<tr>
<td>Wash 2 buffer volume</td>
<td>Greater than 3 CV is needed for optimal performance, little yield loss seen with extended washing.</td>
<td>Action (PP)</td>
</tr>
<tr>
<td>Elution buffer pH</td>
<td>pH range important to get adequate desorption, too low pH results in product degradation/aggregation</td>
<td>Acceptable (CPP)</td>
</tr>
<tr>
<td>Flow rate / residence time</td>
<td>No effect seen over a wide range of flow rates</td>
<td>No Range (MP)</td>
</tr>
<tr>
<td>Elution pool volume</td>
<td>No product impact, no yield impact, indicative of too high pH and/or poorly packed column.</td>
<td>Alert (PA)</td>
</tr>
<tr>
<td>Pool DNA / HCP</td>
<td>Relates directly to CQA</td>
<td>Acceptable (CPA)</td>
</tr>
<tr>
<td>Bioburden / Endotoxin</td>
<td>Microbial control</td>
<td>Action or Acceptable</td>
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# IPC Nomenclature Best Practices – Protein A

## Viral Clearance

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<td>Column characteristics (bed height/HETP/As)</td>
<td>Data shows wide range of acceptable values, separation relatively insensitive to bed height and HETP. Minimum bed height needed to ensure viral clearance.</td>
<td>Alert (PP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acceptable (CPP)</td>
</tr>
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<td>Equilibration / Wash 1</td>
<td>Data shows buffer pH, conductivity, and volume have little effect on step performance</td>
<td>Alert (PP)</td>
</tr>
<tr>
<td>Protein Load</td>
<td>Overloading results in yield loss but no increase in pool impurity levels. Maximum tested protein load becomes criteria to ensure adequate clearance</td>
<td>Acceptable (CPP)</td>
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<td>Wash 2 buffer pH</td>
<td>Optimal performance is within a narrow pH, adequate performance is over a wider pH range. Large effect downstream on subsequent step</td>
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<td>pH range important to get adequate desorption, too low pH results in product degradation/aggregation</td>
<td>Acceptable (CPP)</td>
</tr>
<tr>
<td>Flow rate / residence time</td>
<td>No effect seen over a wide range of flow rates. Residence time often needed to ensure adequate clearance.</td>
<td>Action (PP)</td>
</tr>
<tr>
<td>Elution pool volume</td>
<td>No product impact, no yield impact, indicative of too high pH and/or poorly packed column.</td>
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IPC Nomenclature Best Practices

• Should variables have multiple ranges?
  - No nested ranges

  ![Diagram showing acceptable range, action range, and setpoint]

- CPP with acceptable range
- Also has action range (aka operating range)
- And a setpoint
IPC Nomenclature Best Practices

- No nested ranges

- CPP with acceptable range
- And a setpoint
IPC Nomenclature Best Practices

• No nested ranges

- CPP with acceptable range
- And a target (not controlled)
IPC Nomenclature Best Practices

• Easy to follow (decision tree)
IPC Nomenclature Best Practices

• Be defendable
  - Process Development / Characterization Data
  - Risk assessments
  - Manufacturing history
  - Implementable
    - MBRs
    - SOPs
    - Quality Directives
IPC Nomenclature Best Practices

• What would be considered “best practice”?
  - Should include both inputs and outputs
  - Needs to be multi-tiered
    - Direct links to quality and process performance if applicable to support classification
  - No nested ranges
    - Each variable has only one classification
  - Easy to follow (decision tree)
  - Be defendable/implementable
## IPC Nomenclature Best Practices

<table>
<thead>
<tr>
<th>Classification</th>
<th>Range Description</th>
<th>Deviation Response / Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical Performance Attribute (CPA)</td>
<td>Acceptable Range</td>
<td>In-process result where confirmed excursions are investigated for product impact and likely results in lot rejection</td>
</tr>
<tr>
<td>Performance Attribute (PA)</td>
<td>Action Range</td>
<td>In-process result where each excursion is investigated to determine process performance impact</td>
</tr>
<tr>
<td></td>
<td>Alert Range</td>
<td>In-process result where a pre-designated subset of excursions (ex, 2 out of 5) is investigated to determine process performance impact</td>
</tr>
<tr>
<td>Monitored Attribute (MA)</td>
<td>N/A</td>
<td>In-process outputs that do not have established ranges, and results are reported, trended, and monitored</td>
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<tr>
<td>Critical Process Parameter (CPP)</td>
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Conclusion

• What would be considered “best practice”?
  - CPP/CPA that affect an CQA
  - PP/PA that affect process performance
    - Action ranges
    - Alert ranges
  - MP/MA without control ranges
La Fine

Thank You