The Role of Quality Risk Management in New Drug Development and Manufacturing: Biotechnology Products

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Practical Applications of Quality Risk Management
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Historical Approaches
Pre-QbD/QRM Risk Assessments in Biotech

ICH Guidances

• Q5a: The acceptability of cell lines containing viruses other than endogenous retroviruses will be considered on an individual basis by the regulatory authorities, by taking into account a risk/benefit analysis…

• Q5d: Regarding the generation of cell substrates, applicants should provide a thorough discussion of procedures which would provide exposure to infectious agents…This information…will be part of the risk-benefit analysis of the product.
Historical Approaches
Pre-QbD/QRM Risk Assessments in Biotech

Publications

• **Adventitious Agents from Animal-Derived Raw Materials – a Method of Risk Assessment** (Foster, Dev Biol Stand, 1996)
  - Worksheet developed by Hyclone
  - Total Risk = Recipient Risk + Raw Material Risk
  - Recipient Risk includes age, health status, etc.
  - Raw Material Risk includes scores for
    – Geographic origin, (including traceability, # of companies in supply chain)
    – Animal donor (including animal age, anatomical origin of material)
    – Animal husbandry (including feeding and health care)
    – Harvesting, Handling & Final Preparation (including adv. agent reduction)
    – How RM used in manufacturing process (e.g. upstream vs downstream)
  - High Total Risk scores indicate need for additional processing of the Raw Material
Historical Approaches
Pre-QbD/QRM Risk Assessments in Biotech

Publications
• **A Rational, Step-Wise Approach to Process Characterization** (Seely & Seely, BioPharm, 2003)
• Goal to provide:
  – an understanding of the role of each process step, such as where impurities are cleared during a particular purification step
  – an awareness of the effect of process inputs (operating parameters) on process outputs (performance parameters) and identification of key operating and performance parameters
  – assurance that the process delivers consistent product yields and purity in all operating ranges
  – acceptance parameters for in-process performance parameters.
• Use FMEA on each unit operation to assess the effect and likelihood of an excursion from operating ranges
### Table 1. A risk priority number (RPN) rating system for rating process characterization parameters for use in failure mode and effects analysis (FMEA) (9).

<table>
<thead>
<tr>
<th>RPN Scale</th>
<th>Severity</th>
<th>Occurrence(^a)</th>
<th>Detectability</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;BAD&quot;</td>
<td>Fails final product specifications &gt;90% of the time. Product lost or completely unrecoverable.</td>
<td>&gt;50%</td>
<td>Defect is not detectable</td>
</tr>
<tr>
<td>10</td>
<td>Fails in-process performance parameters 100% of the time, and final product specifications fail &gt;50% of the time. More than 50% effect on step and overall yield.</td>
<td>10–20</td>
<td>Occasional checks for defects</td>
</tr>
<tr>
<td>9</td>
<td>Fails in-process performance parameters ~75% of the time, and final product specifications fail &gt;25% of the time. Approximately 50% effect on step yield, and &gt;25% effect on overall yield.</td>
<td>6–9</td>
<td>Systematic sampling and inspection</td>
</tr>
<tr>
<td>8</td>
<td>Fails in-process performance parameters ~50% of the time. Final product purity specifications fail &gt;10% of the time. Approximately 30–40% effect on step yield, and &gt;25% effect on overall yield.</td>
<td>5</td>
<td>All units are manually inspected</td>
</tr>
<tr>
<td>7</td>
<td>Fails in-process performance parameters ~50% of the time. May fail final product specifications 5% of the time. Approximately 25% effect on step yield, and &gt;10% effect on overall yield.</td>
<td>2–3</td>
<td>Manual inspection with mistake-proofing</td>
</tr>
<tr>
<td>6</td>
<td>May fail in-process performance parameters ~25% of the time. May fail final product specifications 5% of the time. Approximately 25% effect on step yield, and &gt;10% effect on overall yield.</td>
<td>1</td>
<td>SPC(^b) monitoring and manual inspection</td>
</tr>
<tr>
<td>5</td>
<td>Runs on edge of in-process performance parameters, and may fail these ~10% of the time. Approximately 10% effect on step yield, and measurable effect (~5%) on overall yield.</td>
<td>1 lot every two years</td>
<td>SPC(^b) with immediate reaction to special causes</td>
</tr>
<tr>
<td>4</td>
<td>More measurable effect on step yield (5%).</td>
<td>1 lot every 3–5 years</td>
<td>SPC(^b) with 100% inspection for special causes</td>
</tr>
<tr>
<td>3</td>
<td>Slightly measurable effect on in-process performance parameters. Slight but measurable effect on step yield (&lt;3%).</td>
<td>1 lot every 5+ years</td>
<td>All units are automatically inspected</td>
</tr>
<tr>
<td>2</td>
<td>Goes unnoticed.</td>
<td>Never or every 10+ years</td>
<td>Defect is obvious and cannot affect anyone</td>
</tr>
<tr>
<td>1</td>
<td>Not detected; no effect on performance.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)In lots per year, unless otherwise described.  
\(^b\)Statistical process control.
Historical Approaches
Pre-QbD/QRM Risk Assessments in Biotech

Technical Report
• **Process Validation of Protein Manufacturing (PDA Technical Report No. 42, 2005)**
• Quality risk assessment should examine unit ops that may affect safety, identity, strength, quality and purity including those impacting:
  – Viral Clearance
  – Bioburden reduction/removal
  – Glycoform distribution
  – Product purity
  – Product integrity (e.g. c/c)
  – Product stability
  – Product homogeneity (e.g. mixing)
Although there are some examples of the use of quality risk management in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer.

This guidance provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.

These aspects include development, manufacturing, distribution, inspection, and submission/review processes throughout the lifecycle of drug substances, drug products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials…)}
Key Steps in Implementation of QbD for a Biotech Product

Identify TPP → Identify CQA → Risk assessment

Define product design space

Define process design space → Risk assessment

Refine product design space → Process characterization

Define control strategy → Risk assessment

Define control strategy → Process validation

Process monitoring

Filing

Rathore and Winkle, Nature Biotechnology, 27:26-34, 2009
Definitions

• Quality (J. Woodcock, 2004)
  – “Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes.”

• Quality Attribute (Q5e, 2005)
  – “A molecular or product characteristic that is selected for its ability to help indicate the quality of the product. Collectively, the quality attributes define identity, purity, potency, and stability of the product, and safety with respect to adventitious agents. Specifications measure a selected subset of the quality attributes.”

• Critical Quality Attribute (Q8R1, 2008)
  – 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. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product.
Potential CQAs for Biotechnology Products*

- STRENGTH
- POTENCY
- STERILITY
- SIZE
- ADVENTITIOUS AGENTS
- POST-TRANSLATIONAL MODIFICATIONS
- AGGREGATION
- ISOELECTRIC POINT
  - (Charge distribution)
- IMPURITIES (E.G., DNA, HOST CELL PROTEINS)
- FORMULATION COMPONENTS
  - Appearance, particulates, identity

* From Summary of AAPS Workshop, 2004
### CQAs for mAb DS: 2008 Public QbD Proposals

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Company 1</th>
<th>Meeting sum</th>
<th>Company 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color, Clarity</td>
<td>QA</td>
<td>QA</td>
<td>Not included</td>
</tr>
<tr>
<td>pH</td>
<td>QA</td>
<td>CQA</td>
<td>CQA</td>
</tr>
<tr>
<td>[Protein]</td>
<td>QA</td>
<td>CQA</td>
<td>CQA</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>CQA</td>
<td>CQA</td>
<td>CQA</td>
</tr>
<tr>
<td>Bioburden</td>
<td>CQA</td>
<td>CQA</td>
<td>CQA</td>
</tr>
<tr>
<td>Protein A</td>
<td>CQA</td>
<td>CQA</td>
<td>CQA</td>
</tr>
<tr>
<td>HCP</td>
<td>CQA</td>
<td>CQA</td>
<td>CQA</td>
</tr>
<tr>
<td>DNA</td>
<td>Not included</td>
<td>CQA</td>
<td>CQA</td>
</tr>
<tr>
<td>Culture Components</td>
<td>Not included</td>
<td>CQA</td>
<td>CQA</td>
</tr>
<tr>
<td>Low MW fragments</td>
<td>CQA</td>
<td>Not included</td>
<td>CQA</td>
</tr>
<tr>
<td>High MW</td>
<td>CQA</td>
<td>CQA</td>
<td>CQA</td>
</tr>
<tr>
<td>Product-related variants</td>
<td>QA – Sub.</td>
<td>CQA – Imp.</td>
<td>QA**</td>
</tr>
<tr>
<td>Identity</td>
<td>QA</td>
<td>QA</td>
<td>QA</td>
</tr>
<tr>
<td>Potency</td>
<td>CQA</td>
<td>CQA</td>
<td>Not included</td>
</tr>
</tbody>
</table>
ICH Q9: Quality Risk Management

• Annex II – Potential Applications of Quality Risk Management
  – II.3 Quality Risk Management as Part of Development
    • To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8)
    • To assess critical attributes of raw materials, solvents, active pharmaceutical ingredient (API) starting materials, APIs, excipients, or packaging materials
DEPARTMENT OF HEALTH AND
HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–N–0355]

Submission of Quality Information for
Biotechnology Products in the Office
of Biotechnology Products; Notice of
Pilot Program

AGENCY: Food and Drug Administration,
HHS.
OBP QbD Pilot Program

• For Original and Post Approval submissions regulated by OBP (limited number)
• May involve the entire process or focus on a specific unit operation
• Provides enhanced reviewer access
• Focus on defining clinically relevant product attributes and their link to process parameters
• Should use expanded change protocols
• Submit written and electronic requests to participate in the pilot program by September 30, 2009.
Applications to the OBP Pilot: CQAs

• Company A: Initial CQA selection based on prior knowledge for mAb SAR, then FMEA used to rank attributes
• Company B: Identify CQAs using Risk Ranking and filtering
• Company C: Risk Ranking and Filtering used to identify pCQAs; Additional SAR studies performed to refine CQAs
• Company D: QTPP listed; CQA’s not discussed.
• Company E: Quality Attributes are rank ordered based on severity and uncertainty
• Company F: Preliminary CQAs listed; no tool proposed.
Decision criteria to include Severity in addition to S x O?

What is referenced by occurrence? (See next slide)

“Complex quantitative models may convey a level of precision and understanding about the system that is unjustified.” (Claycamp, 2004)
CQAs and Probability: P1, P2 or P3?

**Hazard**: The potential source of harm

**Hazardous Situation**

**Harm**: Damage to health, including the damage that can occur from loss of product quality or availability.

**Severity of Harm**

**Probability of Occurrence of Harm**: P1 x P2

**RISK**: P1 x P2
Using RRF Results: Filtering

Example of a “risk-based” filter

Example of a “resource-based” filter

From Claycamp, 2004
Some questions/observations based on proposals for categorizing attributes

- Decision trees and QRM tools. Is there a preferred tool?
- Should process capability be considered when categorizing attributes?
- How many categories? Binary (critical or not) versus other (intermediate category, graded scale)
- How should prior knowledge be incorporated?
- What level of confidence / type of study is needed to identify an attribute as non-critical?
- Most have included safety/efficacy impact as relates to
  - Safety (± Toxicity)
  - Efficacy (± Biological activity)
  - PK (± PD)
  - Immunogenicity
Acknowledgements

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