Implementing Risk Assessment Tools for Identifying Critical Raw Material Attributes
Background

..the manufacture of a biological product of defined quality relies on thorough description, characterization, and testing that begins with source materials, reagents, ingredients and components used throughout the manufacturing process. (Dr Fink, CBER)

The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. (ICH Q10)
Issue:

Need for a risk-based, phase appropriate means to define critical quality attributes for raw materials.

A process that:

- Identifies and ranks risk components for raw materials
- Allows for platform specific raw material control strategies
- Information to streamline change control, deviation resolution and regulatory management
Bioprocessing Activities and Raw Materials

- Cell Line Development
- Cell Banking
- Cell Culture
- Primary Recovery
- Purification (chromatography)
- Final TFF step
- Seed Train Production Reactor
- Excipient Components

Buffers
- Media and feeds
- Amino acids
- Electrolytes
- Metabolic components
- Processing aids

Buffers
- Chromatographic resins
- Electrolytes
- Viral inactivation additives
- API stability enhancers
Raw Material Control Issues

What attributes of the raw materials are important to the final biological product?
- When do we invest in characterizing the materials?
- What properties are critical to control for both the user and supplier?

How do we identify information requirements and criteria for efficient study designs that are meaningful for both development and commercial manufacturing?
- What raw material characteristics are important to evaluate when the biological product process is modified?
- What characteristics are important to evaluate when the raw material process is modified?

How do we share information between development projects and the eventual commercial manufacturing sites?
- How do we capture and use risk assessments?
Quality Risk Management Approach (ICH Q9)

Initiate Quality Risk Management Process

Risk Assessment
- Risk Identification
- Risk Analysis
- Risk Evaluation

Risk Control
- Risk Reduction
- Risk Acceptance

Risk Review
- Review Events

Identification:
Gather Information about process and raw materials

Analyze Raw Material Risks/
Establish Risk Level

Evaluate Raw Materials with
High Level Risks

Risk Management Tools
Raw Material Information – Risk Assessment

1. Potential to impact the drug substance quality
2. Ability to introduce bioburden, endotoxins, or viral contaminants (Adventitious Agent Assessment Strategy).
3. Historical knowledge of the raw material
4. Raw material molecular complexity
5. Safety and handling
6. Vendor experience
7. Custom raw materials
8. Area of use in the process
9. Is the raw material primarily manufactured for the pharmaceutical industry?
### Raw Material Risk Assessment Tool

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<table>
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<th>Description</th>
<th>Vendor</th>
<th>Intended Use</th>
<th>Reasons for ranking risk</th>
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**Cell Culture**

**Purification**

**Final API**
## Comparison between products

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Benefits of Raw Material Assessment

• Consistency in assessment approaches

• Leadership understands level of risk between products and processes

• Information leading to meaningful development study designs

• Align discussions and expectations between development groups

• Cost savings in Development’s time

• Alignment of development process with QbD guidance
Raw Material Risk Assessment’s Role in Product Development

Ref: Guillermo Miroquesada, (Eli Lilly)
Quality Risk Management Approach (ICH Q9)

- **Risk Assessment**
  - Risk Identification
  - Risk Analysis
  - Risk Evaluation

- **Risk Control**
  - Risk Reduction
  - Risk Acceptance

- **Risk Review**
  - Review Events

- **Risk Management Tools**
  - Identification: Gather Information about process and raw materials
  - Analyze Raw Material Risks/Establish Risk Level
  - Evaluate Raw Materials with High Level Risks
  - Propose Mitigation/Control Plans

- **Output / Result of the Quality Risk Management Process**
### Example: Cell Culture Media

#### Bioprocess and Analytical Needs:
- Consistent desired quality
- Appropriate stability
- Fits development platform with acceptable product yield
- Understanding of how media quality impacts the pharmaceutical product

<table>
<thead>
<tr>
<th>Description</th>
<th>Vendor</th>
<th>Product quality</th>
<th>Bioburden: endotoxins, viral contaminants</th>
<th>Poor History</th>
<th>Molecular complexity</th>
<th>Safety and handling</th>
<th>Company Experience with Vendor Custom Raw Materials</th>
<th>Area of use</th>
<th>Mfg for pharma industry</th>
<th>Combined Rating</th>
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CMC Strategy Forum, Jan 11, 2009

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Robustness & Optimization Example

Continuous factors centered by mean, scaled by range/2

Term                  Scaled Estimate  Std Error  Prob>|t|
Intercept             2.44          0.10       <.0001 *
Temp                  0.98          0.09       <.0001 *
D3 Feed (X)           -0.47         -0.08      <.0001 *
Feed (X)              -1.90         -0.14      <.0001 *
D9 Feed (X)           -0.42         -0.10      <.0001 *
pH                    0.48          -0.10      <.0001 *
(Seed Density (Meas)-1.29778)*(Temp-34.75) 0.59          -0.22      0.0100 *
(Seed Density (Meas)-1.29778)*( Feed (X)-473.25) 1.05          -0.25      0.0001 *
(Seed Density (Meas)-1.29778)*(Day of Culture-15.5) 0.36          -0.10      0.0005 *
(Temp-34.75)*( Feed (X)-473.25) -1.30         -0.14      <.0001 *
(D3 Feed (X)-1.4)*( Feed (X)-473.25) 1.12          -0.11      <.0001 *
(D3 Feed (X)-1.4)*(Day of Culture-0.6) 0.41          -0.09      <.0001 *
(D3 Feed (X)-1.4)*(Day of Culture-15.5) -0.19         -0.07      0.0125 *
(  Feed (X)-473.25)*( Feed (X)-473.25) 2.46          -0.17      <.0001 *
### Example: Alignment of Raw Material with Product Critical Quality Attributes

<table>
<thead>
<tr>
<th>Modification</th>
<th>Likely Source of Modification</th>
<th>CQA</th>
<th>Raw Material</th>
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<tbody>
<tr>
<td>N-terminus Pyruvylation</td>
<td>Bioreactor</td>
<td>High</td>
<td>Media components</td>
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<tr>
<td>Oxidation</td>
<td>Bioreactor and purification</td>
<td>High</td>
<td>Growth additive</td>
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<tr>
<td>Deamidation</td>
<td>Bioreactor and purification</td>
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<tr>
<td>Glycosylation</td>
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<td>Growth additive</td>
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<tr>
<td>Free Sulfhydryl</td>
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<td>Low</td>
<td>None</td>
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<tr>
<td>Glycation</td>
<td>Bioreactor</td>
<td>Low</td>
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</tr>
<tr>
<td>Aggregation</td>
<td>Purification steps and storage</td>
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<td>Resin</td>
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Ref: Kozlowski & Swann  
## Cell Culture Media: Specification Development

### Baseline Specifications

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<th>Physical Evaluation</th>
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<tr>
<td>Packaging Appearance</td>
<td>Visual</td>
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<td>Physical Appearance</td>
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<td>Identification Test</td>
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<td>Spectroscopy</td>
<td>NIR, Raman</td>
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<td>Suitability Test</td>
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<tr>
<td>Growth Promotion</td>
<td>Null strain</td>
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<td>Other Tests</td>
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<tr>
<td>Endotoxin</td>
<td>USP</td>
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### Extended Specifications (Example)

<table>
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<th>Physical Evaluation</th>
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<td>Packaging Appearance</td>
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<td>Endotoxin</td>
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<tr>
<td>Bioburden</td>
<td>USP</td>
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<tr>
<td>Sterility</td>
<td>USP</td>
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Phase Appropriate Development

- Provide list of raw materials used in process
- Quality Assurance Review
  - ASMs, vendor audits/qualification, etc.
- Assess raw material risk elements using RMAT
  - No requirement for commercial appropriateness
  - Identify potential need for alternate sources of High Risk raw materials
- All raw materials in Materials and Laboratory Information Management Systems
Phase Appropriate Development

- Reassess raw material risk elements to incorporate knowledge from additional processing experience
  - Risks incorporate commercial manufacturability
- Control strategy for High Risk raw material’s known and evaluated for suitability for current process
- Assessment of raw materials in collaboration with potential manufacturing site for suitability, availability, handling and disposal.
- Preliminary rationale for “Intended Use”
Critical Quality Attributes of high risk raw materials defined using tools such as:

- Literature Review
- Data Mining (e.g. previous manufacturing of this molecule)
- DOE’s (including multiple lots of high risk raw materials as necessary)
- Prior knowledge based on platform

Defined Process – Final list of raw materials

- With rationale for “Intended Use”
- Consider all potential raw materials and sources
Phase Appropriate Development

- Raw material specifications identified and linked to product quality attributes
- Finalize sourcing strategy with manufacturing site
- Develop vendor qualification and change management strategy
- All raw materials in Manufacturer’s Information Management Systems
- Transfer raw material analytical methods to manufacturing site
- Raw material control strategy documentation finalized
Phase Appropriate Development

Start
Q1
Q2
Q3
Q4
Pre-IND
Q1
Q2
Q3
Q4
Decision
Q1
Q2
Q3
Q4
Registration Stability
Q1
Q2
Q3
Q4
Mfg Scale
Q1
Q2
Q3
Q4
Launch

Initial RMAT
Platform knowledge

RMAT review
Small scale studies
Handling/storage information
QA information

Cause-Effect data
Medium scale studies

FMEA update
Raw Matl CQA’s
Sourcing Strategy
Example: Raw Material Risk Process and Impact to Change Management

Functionality
- Development determined risk levels (tool)
- What is predicted impact to product CQAs?

Complexity
- How well is the compound known?

Magnitude of change
- Process Technical Services review of changes/qualifications
- Facility/process change
- Raw material change
- New supplier
In Summary…

In order to develop a successful manufacturing process that:

• ensures reproducible and consistent product
• defined quality suitable for commercial distribution
• supports complex and novel platform technologies create greater, more varied number of product development issues

Setting up a proactive system for raw materials qualification ensures a constant supply of materials of appropriate quality and enhances the safety and consistency of a pharmaceutical product.
Questions?