Background

- Today’s presentation features key lessons learned from the presenters’ recent experiences training FDA product reviewers on Quality Risk Management (QRM)
- These contents are reflective of informal FDA feedback and should not be interpreted as formal guidance or FDA positions
- The intent is to focus attention on areas where industry may significantly improve performance of QRM and increase the confidence that all regulators have in risk-based approaches and deliverables
Key Themes in FDA Feedback

1. Transparency
   - A clarity, openness, and specificity, which allows reviewers to understand how inputs (data, scientific reasoning) ultimately support risk-based conclusions

2. Objectivity
   - A commitment to impartiality through science and data-driven decision making

3. Decision Making
   - Ensuring risk management decisions are rooted in transparent and objective analyses

4. Documentation & Communication
   - Concise manner by which we convey comprehensive risk management decisions and conclusions in a fashion that preserves and demonstrates the transparency and objectivity of the exercised QRM process
Transparency: FDA Feedback

- **ICH Q9 Risk Assessment Phase:**
  - Risk Ratings and Thresholds: Common Problems
    - Inability to understand how certain risks were scored
      - Inexplicably too high / low
      - Inconsistency with similar risks
    - Ambiguity – Poorly worded rating scales that do not convey clear and logical differences between risk levels
    - Thresholds and ratings poorly justified or explained
      - Thresholds need to make sense in the context of the actual risks
  
- **ICH Q9 Risk Control Phase:**
  - Residual risk acceptance: Transparency is key to…
    - Understand the thought-process and justification for acceptance of elevated risks
    - Who ultimately accepted the residual risk?
  - Industry risk acceptance : Areas noted by FDA for improvement
    - When there is no justification for why heightened risks were accepted
    - When industry’s risk acceptance process is not transparent to FDA (how risks are accepted and justified, who is involved, etc.)
Transparency: Enhancing Regulators’ Confidence

Rating scale should be tailored to:
- Project scope
- Problem statement
- Product impact
- Qualitative versus quantitative
- Data availability

Rating scale should work for the problem statement:
- Provide true differentiation of risks, driving appropriate risk control
- Generate a meaningful distribution of risks across the assessment

Rating scale can be qualitative or quantitative:
- Ratings do not need to be quantitative to be effective
- Qualitative 3-level scales (ex: Low / Medium / High) can yield good distributions of risks
Objectivity: FDA Feedback

• ICH Q9 Risk Assessment Phase:
  – Risk Thresholds:
    • May be set either before or after risk data is generated, so long as they are justifiable and transparent
    • Should primarily be established based on the problem statement

• ICH Q9 Risk Control Phase:
  – Risk Acceptance:
    • Industry risk acceptance: Areas noted by FDA for improvement
      – Borderline risk acceptance decisions based on hard thresholds and heat maps
        • Consider the risks just below the threshold(s)
        • Provide rationale into risk acceptance as opposed to a disjunctive risk acceptance or rejection based merely on a threshold
    • Concepts of right-sizing vs. down-sizing
      – Entering into QRM with a mindset of ‘right-sizing’ of controls is sensible
      – Entering into QRM with a mindset of ‘down-sizing’ of controls is dangerous
Objectivity: Enhancing Regulators’ Confidence

• Risk Thresholds & Acceptance:
  – Thresholds rooted in objective criteria make decision making more effective
    • Patient / consumer health, safety, comfort outcomes
    • Movement within or outside layers (PAR, NOR) of the design space
  – Risk thresholds: Should generally not be based on arbitrary safety factors or unrelated sources
    • “80/20 rule” or similar
    • Thresholds set for other unrelated studies
  – Risk acceptance and right-sizing of risk controls is more simple and defendable when rooted in objective criteria
• **ICH Q9 Risk Assessment Phase:**
  – Risk Thresholds: Common Problems
    • Absence of thresholds – no rationale around how the sponsor decided what was acceptable or unacceptable
    • Thresholds sometimes taken too literally
      – Acceptance of risks that are below, but near the threshold
      – Decisions made solely with respect to a hard threshold

• **ICH Q9 Risk Control Phase:**
  – Industry risk control: Areas noted by FDA for improvement
    • When patient impact does not seem to be central to the decision making
      – Mention of business-related benefits in support of risk acceptance
    • Over-reliance on human performance
• **Heat Maps must be carefully managed**
  - Simplicity is powerful when backed by transparent and appropriate justification
  - Contours may be different for each study

• **Residual risk acceptance**
  - Explain risk acceptance rationale for risks which are:
    - Obviously heightened
    - Near or at critical thresholds
    - High severity yet low probability risks

![Heat Map Diagram]

<table>
<thead>
<tr>
<th>Severity</th>
<th>Probability of Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Catastrophic</td>
</tr>
<tr>
<td>8</td>
<td>Critical</td>
</tr>
<tr>
<td>6</td>
<td>Serious</td>
</tr>
<tr>
<td>4</td>
<td>Significant</td>
</tr>
<tr>
<td>2</td>
<td>Negligible</td>
</tr>
</tbody>
</table>
• **ICH Q9: Risk Outputs**
  
  – What is commonly missing from risk assessments submitted to FDA?
    
    • Why the risk assessment is being performed
    
    • Details around:
      
      – Scope – what’s in scope and an explanation if related risks are out of scope
      
      – Rationale behind tool selection
      
      – Level and types of data used in the assessment
      
      – Threshold justification
    
    • Context around lifecycle considerations (for product risk assessments), including linkage to any earlier or future risk assessments
    
    • Explanation around any risk scores that seem counter-intuitive
      
    – **Feedback from other global Boards of Health**
• For risk assessments that directly support a regulatory submission to FDA:
  – An appropriately redacted summary report of the risk assessment is most often the best option
  – Generally discouraged:
    • Just briefly mentioning that a risk assessment was performed, or
    • Submitting the entire detailed risk assessment (unless specifically requested)

• Proactive engagement of FDA encouraged
• Documented evidence that a risk assessment may have led you to explore an alternative approach
Conclusions

- Careful attention in the following areas may increase regulators’ confidence in your QRM work products:
  - Objectivity
  - Transparency
  - Decision making
  - Documentation
  - Communication
Acknowledgements

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