Enhancing Regulators' Confidence in your Quality Risk Management Work Products

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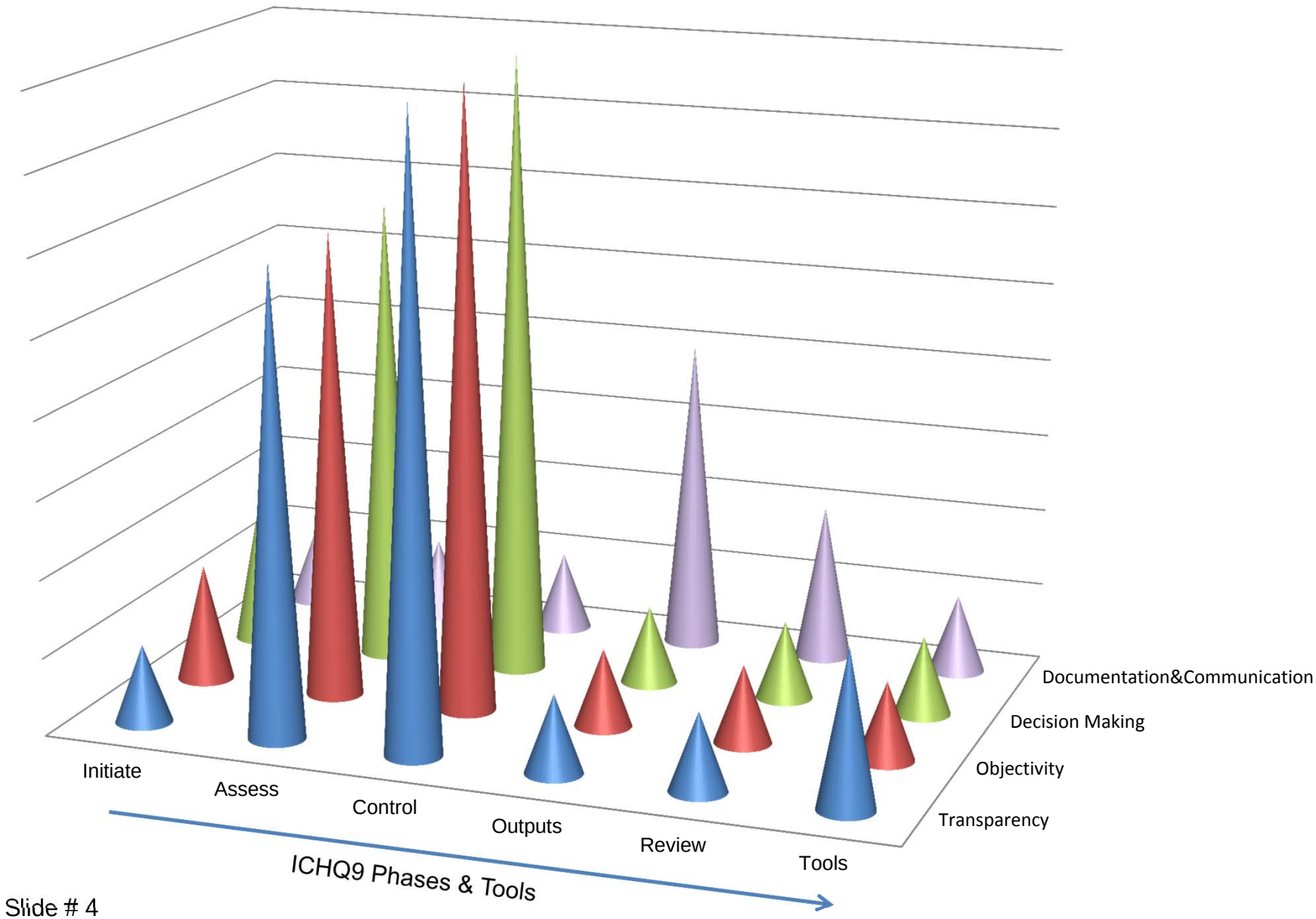
Background

- **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**

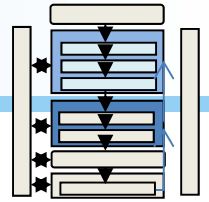
Key Themes in FDA Feedback

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

Topographical Map of FDA Feedback



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

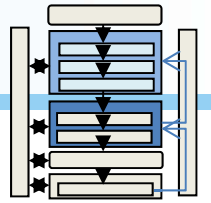
Rating scale should work for the problem statement

- 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

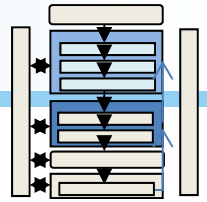


- **ICH Q9 Risk Assessment Phase:**
  - Risk Thresholds:
    - May be set either before or after risk data is generated, so long as they are justifiable and transparent
    - Should primarily be established based on the problem statement
- **ICH Q9 Risk Control Phase:**
  - Risk Acceptance:
    - Industry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

Decision Making: FDA Feedback



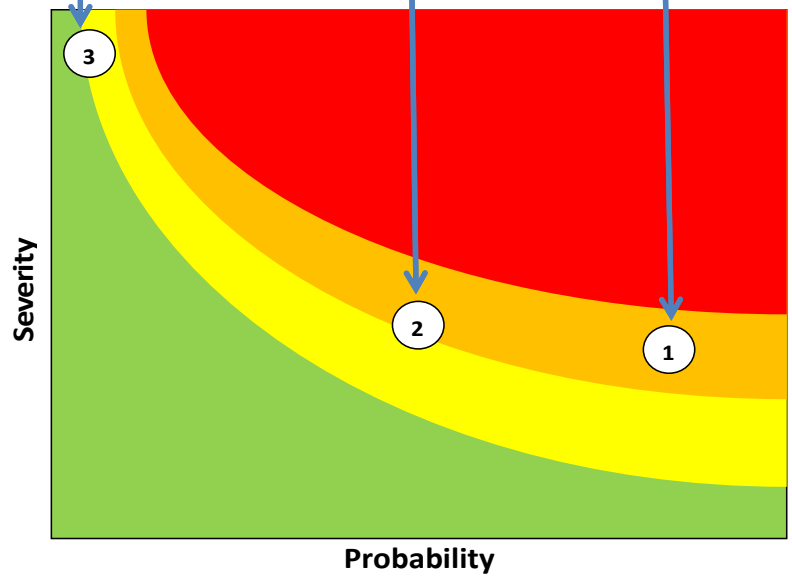
- **ICH Q9 Risk Assessment Phase:**
  - Risk Thresholds: Common Problems
    - Absence of thresholds – no rationale around how the sponsor decided what was acceptable or unacceptable
    - Thresholds sometimes taken too literally
      - Acceptance of risks that are below, but *near* the threshold
      - 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

Decision Making: Enhancing Regulators' Confidence

- **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

			Probability of Occurrence				
			2	4	6	8	10
Severity	10	Catastrophic					
	8	Critical	16				
	6	Serious					
	4	Significant		16			
	2	Negligible				16	



Documentation & Communication: FDA Feedback

- **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

Documentation & Communication: Enhancing Confidence

- **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

- **Kristin Murray, Associate Director, GCMC Regulatory Affairs, Pfizer**