Table 2: Best Practices for QbD Development of Analytical Methods

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<th>Session 1:</th>
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<tr>
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**SCOPE:**
Development of robust analytical methods and life-cycle management has been a crucial part of pharmaceutical drug development. Concepts of Quality by design (QbD) are increasingly being used to help improve the robustness of manufacturing processes and to facilitate continuous improvement to enhance product quality and manufacturing productivity. Usefulness and advantages of the QbD methodology as an adaptive optimization tool has been recognized by both industry and regulators. Key concepts have been described in International Conference on Harmonization (ICH) guidelines Q8(R1) *Pharmaceutical Development*, Q9 *Quality Risk Management*, and Q10 *Pharmaceutical Quality System*.

QbD for analytical methods (aQbD) matches QbD for manufacturing processes. Many of the concepts associated with QbD for the manufacturing processes can be similarly applied for analytical method development, e.g. upfront definition of the objectives, focus on scientific knowledge, use of risk-based approach, make the process iterative and development of appropriate tools. Scope of this table is to discuss various approaches and best practices for development of analytical methods utilizing QBD concepts.

**QUESTIONS FOR DISCUSSION:**
1. aQbD is a mindset: which of the major concepts (as upfront definition of the objectives, focus on scientific knowledge, use of risk-based approach, make the process iterative and development of appropriate tools) is more widely applied in your routine experience? can they work separately?

2. When to apply aQBD. Is it beneficial in all situations or only in some cases?

3. How to utilize aQBD for new methods and for lifecycle management. For some specific technologies, is it really needed to go through the entire aQbD based development or some steps can be skipped based on prior knowledge?

4. VOC and knowledge transfer: how to make the iterative aQbD process working through the interface between development space and QC operations?

5. Potential regulatory flexibility (e.g. post-approval change management) through aQbD
DISCUSSION NOTES:

QbD is a mindset – what are major elements already applied?
- Initial method risk assessment to decide critical factors. Try to explain where they came from.
- Some start with platform methods which did not come out of QbD
- Is some of this a structured way to describe what you have been doing before?
- Establish the process starting with the analytical target profile.
- Start with a wish list which may be technologically driven
- Sometimes hard to develop a technique that will span different levels of concentration?
- May have different ATP for different situations.
- What about methods that may be new to an Agency?
- Also need to worry about new methods and what they might uncover that older methods did not show.

When to apply QbD? Is it beneficial in all solutions or only in some cases?
- Know how your method performs and what can change performance?
- Bioassay method development is more amenable to QbD?
- For chromatography, different columns over times may be a challenge.
- Knowledge of design space of methods can be helpful.
- For looking at columns, may need to look at multiple lots (at least 3) of columns.

In the interface between development and QC, how is the knowledge transfer informed by or designed by QbD?
- Not really done with quality up front per se.
- May be done with knowledge of what quality group(s) may need.
- Monitor electronically the use of the method throughout lifecycle? Does that help.

Some of QbD has been done in the past, but just not called QbD.
- If method is developed in the correct way, validation becomes a final check off.
• QBD is not just method robustness/DOE, it’s a concept for lifecycle development
  o Look at the data and drive method revision before method validation
• What is ATP for methods and how it is being used across companies
  o ATP includes business and performance issues
  o Selection of method is part of ATP
• Phase appropriate method qualification-some don’t like this classification, -it’s a continuum
• Validation protocol-balance of safety/efficacy requirement vs method capability
• How much regulators have asked for pre-validation development reports. Some responded
  that regulators have started looking at method development/history
• Method development data typically needed especially for CPP
• How much data trending is being performed across method development/performance life-cycle, some do it and some don’t.
• When is method robustness being tested. Robustness is not Ruggedness
• When do and how many lots do you test during method qualification/validation?
  o It really depends on number of lots available