Table 7: Analytical Quality-by-Design (aQbD)

Session 1:	Session 2:
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SCOPE:

Analytical methods are essential for effective drug substance (DS) and drug product (DP) development, process understanding and control, product knowledge, and ensuring product quality during release and stability. Consequently, analytical methods are a significant component of the Quality-by-Design (QbD) paradigm that was introduced under ICH Q8, Q9, Q10 and Q11.

The quality target product profile (QTPP) and critical quality attributes (CQA) define attributes that must be controlled during manufacture for the release of DS and/or DP. An analytical quality by design (aQbD) approach describes the attributes and method performance characteristics that are necessary in an analytical target profile that is established before the initiation of method development, utilizes risk assessments throughout development to ensure sources of variance are mitigated, examines multivariate interactions through Design of Experiments (DoE) to identify robust operating conditions, establishes control of the method by defining the operating design space and system suitability criteria, validates the performance of the method, and ensures the method remains in the validated state through method trending and continuous improvement.

This round table is intended to encourage discussion of the application of QbD elements in the analytical arena and the challenges, constraints and benefits of implementing aQbD.

QUESTIONS FOR DISCUSSION:

1. What is the status of deployment of aQbD in your company? What are the challenges and constraints?
2. What are the benefits of implementing aQbD? Any examples?
3. What type of analytical methods benefit from QbD approach the most? HPLC, CE, icIEF, MS, potency assay, process-related residual (rHCP, rProA) method?
4. Did you apply prior knowledge to reduce the number of experiments during DOE experimental design?
5. What aQbD elements were included in the regulatory filing? Did you receive any feedback from regulatory agencies?
6.

DISCUSSION NOTES:

Session 2:

What is the status of deployment of aQbD in your company? What are the challenges and constraints?

- aQbD is used in method development and parameter assessments. Technique development is challenging when so many things change during development
- Analytical Target Profile

- ATP is a moving target. Defining early stage means you have already aligned method for purpose and this changes over time.
- Guidelines not always clear what to include

Early phase: how much do you invest in DOE?

- Front load DOE because development can move quickly in accelerated programs
- High method variability - do DOE up front, but platform methods take more time with DOE
- Risk assessments allow you to catch knowledge for future implementation.
- Need to tease out Method risk vs CQA risk.
- Measure robustness of methods up front? Methods tend to be snapshot in time. Formal robustness study happens before validation, but also do a pre-robustness study as part of the DOE

Challenging to tie back to clinical relevance

Defining parameters that must be met in order to be appropriate for commercial supply.

This ends up being an approach for platform technology. Platform doesn't mean it is ready- still needs development, but good enough for phase 1

PAT use for continuous manufacturing. But still unclear how to get it approved and agency thoughts beyond QbD

- Lack of Real time decision making slows down PAT use
- Approval in major markets means you still run offline for countries that do not recognize PAT. Hard to harmonize
- Multivariate analysis is a powerful tool for analytics

What are the benefits of implementing aQbD? Any examples?

- If method is better than USP, use it - FDA does not agree with all USP methods (CE-SDS for example is not suitable for mABs)
- Designed a method that was so good that it has enhanced the process, a hold time was no longer needed for in process testing.
- Benefit when a method is so well defined that it allows you to determine if an issue is due to the method or the process.

What type of analytical methods benefit from QbD approach the most? HPLC, CE, icIEF, MS, potency assay, process-related residual (rHCP, rDNA) ELISA method?

- ELISA assays because they are highly variable
- PCR
- Titer as an attribute is important to control
- More complex methods would have more benefit