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Application of Quality by Design (QbD) Principles to Method Validation

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Q8: Pharmaceutical Development

Guidance on how to submit pharmaceutical CTD sections (including the specifications) based on QbD principles

For commercial application, but may be applied as needed in a development setting

Does not specifically address method validation

Not a stand alone document:

- Q9: Risk management
- Design of Experiments (DOE)



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What do I see ?

QbD: Compliance based on Science versus Blind Compliance

QbD: Pro-active versus Re-active Process Management

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Win Win Situation for FDA and Industry!!



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QbD in a nutshell:

The Four Main QbD Principles:

1. Quality cannot be tested in, it must be built in
2. Identify the critical attributes
3. Apply risk management based on sound science
4. Define the design space

The Benefits of QbD:

- Operation within the design space is not considered a change
- Increased flexibility
- Increased speed and decreased cost

????? HOW TO GET THERE ???????? WILL IT BE MORE WORK ?????



When done right: Method Validation is only the confirmation of suitability of use

Better Approach

Common approach

Develop the Method

Validate the Method to check if method is suitable for use

QbD

Set Expectations:
Purpose and deliverables of the method

Develop the Method according to purpose and deliverables

Validate the method, to confirm method is suitable for use

QbD must be applied prior to method validation, during the design and robustness phase!



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Some aspects of Method Development already follow QbD!!!

Quality shall build in:

- Generally originates based on the purpose (measure change variants)
- Method development focuses on separating variants to support safety-efficacy and/or lot consistency testing

Identify Critical Attributes:

- Robustness is performed to identify critical method parameters

Define Design Space:

- Tight control in form of ranges are set in general for all method parameters
- Often including non-critical parameters! (example of Blind Compliance versus Science based Compliance!!)



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But, we are often missing:

1. Documentation of Decision Making/Development Process

- Write development reports- document why the method was optimized to a certain separation condition
- Define not only “measures charge based variants” as purpose
 - Is the measurement of a critical quality attribute based on this method (impact on safety/efficacy) or is it mainly a method to measure lot consistency (all variants have the same potency?).
 - Is this method on the stability protocol? Why?

2. Identification and Classification of Method Parameters as Critical and Non-critical

- Apply DOE in your Robustness and Validation
 - Identify critical parameters based on statistical analysis
 - Eliminate non-critical parameters based on statistical analysis
 - Find potential interactions between parameters
 - DOE when designed correctly will reduce experimental time and increase knowledge!
 - Keep it SIMPLE!



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The method does not operate in a vacuum but is linked directly to the Specifications!

3. Document what is considered a Significant Change (for a commercial application)

- Is there a specific part of the profile that's critical to the quality of the product
- Is it a change in quantitation?
- Is it a change in profile?

4. Outline Plan of Action in case of Significant Changes (for a commercial application)

- Change is inevitable, be prepared.
- Have a planned outline for the most common changes (column, instrument, software)
- At what point does the change warrant a revision of the acceptance criteria

Finally:

5. Use Risk Management Tools to Document your Decision Making Process!



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Example of Risk Management Tool

Per Q9: It is neither always appropriate nor always necessary to use a formal risk management process....

You can design a tool that fits your need!

Method Parameter	Target	Range	Risk	Risk mitigation	Severity [1-10]
Software					
-data acquisition					
-data transfer					
Instrument Parameters					
-focusing time					
-temperature					
Capillary					
Ampholytes					
Sample preparation					



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Final Thoughts

It is not a change on how we approach method development/validation but how we document it

There are clear advantages to following QbD principles

1. Pro-active method management

- The right method from the start
- One development, one validation
- Decreases redundant development efforts and reduces cost

2. Pro-active method lifecycle management

- Change is inevitable, due to vendor changes or transfer activities
- Define critical method parameters to reduce transfer activities and minimize costly re-validation for potential non-critical method changes

3. Post-approval Flexibility

- Reduced Filing Activity
- Increases Speed and Reduces Cost



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Jiaqi Wu

Knowledge and Experience
beats

Blind Experimentation:

Critical parameters to consider during method
optimization/development of iCIEF applications