

FDA's Pharmaceutical Quality Initiatives –
Implementation of a Modern Risk-based Approach
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Modern Approach to Process Validation

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Issues Discussed

1. How do we determine the type and amount of information that will provide sufficient assurance to permit commercial batches to be released to the market?
2. How can a validation program be structured to reflect the level of process understanding and the degree of confidence in the design space? How might the validation program change as process knowledge and understanding increases?
3. Should the validation program apply to changes within a design space? How might it differ than changes outside of the design space?
4. How should risk management be incorporated into the validation lifecycle approach?

Shared Understanding and Agreements

- Validation lifecycle consists of process development, demonstration, and continuous verification
- The three batch approach is not meaningful – sometimes too much, sometimes too little
- Some things have not changed:
 - Identify and control what is critical
 - Use in-process measurements as part of evaluation
 - Demonstrate a state of control
 - Demonstrate reproducibility over time
 - Justify and document changes in controls

Shared Understanding and Agreements

- Process validation confirms the design space and control strategy
 - Often a limited full scale demonstration of knowledge gained at smaller scale
 - Validation program should be dependent upon level of process knowledge and understanding
 - Focus should be on scale dependent aspects that impact CQAs
 - Approach should be flexible and risk-based

Shared Understanding and Agreements

- Risk assessment valuable in establishing validation strategy
 - Identify critical attributes and predict effect of changes
 - Utilize prior knowledge
 - Reduce "over validation" for a well-understood process
- Risk assessment to determine impact of changes on CQA
 - Changes inside design space under Quality System
 - Changes outside of design space may require regulatory filing
 - Need to document and track changes

Remaining Challenges

- Terminology - "validation" means different things to different people
- Concern over regulatory expectations regarding validation
 - Harmonization between global regulatory agencies
 - Application review vs. site inspection?
 - Confusion over implementing traditional vs. new validation paradigm
 - Early agreement of validation program with agency would be useful
- Industry & regulator challenges
 - Knowledge management & communication challenges
 - Reluctance to change
 - Training and expertise
- Implementation challenges
 - Application of statistically based approaches to validation
 - Does commercial scale need to be demonstrated at edges of design space?
 - How much is enough understanding and demonstration?
 - How to apply new paradigm to legacy products?

Recommendations

- Work with other regulatory agencies to harmonize validation expectations
- Issue comprehensive guidance to industry clarifying expectations and approaches
- Training of agency and industry personnel
- Gain experience and refine regulatory approaches