

FDA's Pharmaceutical Quality Initiatives -  
Implementation of a Modern Risk-based Approach

Co-sponsored with AAPS and ISPE  
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Breakout Session F:  
**Quality by Design (QbD): Risk-Based Flexible  
Regulatory Approaches and Regulatory Agreement**

Moderators:

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## Deliverables

- This session seeks to discuss different approaches of regulatory flexibility, the way to approach and document this flexibility, and what type of information would be submitted when those changes occur. Sharing of experiences of those companies and regulators involved with the CMC Pilot Program regarding post approval change mechanisms are envisioned during this session.

## Discussion Point 1

- What kind of regulatory flexibility can you envision (or would you propose) in a QbD application?

## Shared Understanding and Agreements

Regulatory Flexibility includes:

- No post approval filings for:
  - Manufacturing Site Transfers
  - Alternate packaging or packaging sites
  - Alternate analytical methods and testing sites
  - Scale up
  - Movement within the Design Space/Proven Acceptance Ranges
- Replacing end product testing with in process testing

Flexibility is dependent on what is submitted!

## Discussion Point 2

- Will a "regulatory agreement" be useful or necessary to capture the regulatory flexibility? Why or why not?

## Shared Understanding and Agreements

- Yes!
- Not only is it necessary, it is both necessary and useful

WHY?

- Would capture the commitments of industry and FDA
- Will address possible loss of knowledge due to staffing changes
- Encourages life cycle management
- Documents the relationship between Quality Attributes and Design Space

### Discussion Point 3

- What should be the scope (what kind of submissions should it apply to?) of a “regulatory agreement”?

### Shared Understanding and Agreements

Could apply to:

- Original NDAs including:
  - Traditional NDAs
  - NDAs with Design Space information

and

- Legacy Products (i.e. previously approved NDAs)

### Discussion Point 4

- What should be the content of a “regulatory agreement”?
- What should be included in a “regulatory agreement” to facilitate product lifecycle management?

### Shared Understanding and Agreements

Content:

- Identification of the Critical Attributes
- Agreement on the Design Space
- Regulatory reporting mechanism

Lifecycle:

- The changes you envision for the future
- Change control strategy (i.e. the plan and the criteria to evaluate) to be utilized (*Change management strategy*)

### Discussion Point 5

- What are the challenges to the industry when submitting such a proposal? What are the challenges to the FDA when assessing, approving, and enforcing the provisions of such an agreement?

### Shared Understanding and Agreements

Challenge to Industry is:

- How to anticipate all the changes you want from a Life cycle viewpoint
- No current guidance available or case studies
- Getting industry to think differently
- Would it delay approval time?
- If it were a living document, might be challenging to maintain

## Shared Understanding and Agreements (cont)

### Challenge to FDA:

- More upfront work; although may be balanced by fewer supplements
- Possible additional burden for field investigators
- If no information on commercial scale Design Space, then it is a leap of faith for reviewer to agree DS based only on lab/pilot scale experiments

## Remaining Challenges

- No current guidance or case studies
- Would like this to be globally accepted – do we want a timely ICH Guidance??
- Old mindset regarding changes guidances
- Still don't know how much data is needed to support requested flexibility
- Where to keep additional knowledge (gained post submission)
- Where is the RA? Module 1, 2 or 3? Somewhere else?
- Is the content of the RA all encompassing or selective

## Recommendations

- Industry and FDA should work together to move forward the Regulatory Agreement
- Industry and FDA should continue to share experience from CMC pilot program and regulatory agreements
- Case Studies or Mock Regulatory Agreement should be published