

An Industry Perspective on the FDA CMC Pilot Program

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- ❖ Wyeth is participating in the CMC pilot program for the New Drug Application (NDA) review of
 - Product “x” – a modified release, film-coated solid oral dosage form
 - Product “y” -a parenteral dosage form

Selection Criteria

- ❖ High priority projects
- ❖ Stage of development
- ❖ Availability of markers for clinical performance
- ❖ Quality by Design for API and Drug Product

Product x and y

- ❖ Guidances/Documents used to aid QbD Development
 - ICH Q8 –Pharmaceutical Development
 - Establish design space based on scientific/mechanistic understanding of product and process; movement within the design space is not considered a change
 - PAT and design space are fundamentally linked
 - ICH Q9 – Quality Risk Management
 - FMEA, ANOVA, and DOE
 - All analyses outcomes were reviewed and endorsed by a multi-disciplinary team
 - PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance

Product “x”

- ❖ A level A IVIVC has been demonstrated based on FDA guidance
- ❖ Hypromellose is the release-controlling excipient in the formulation
- ❖ On the basis of FMEA and DOE, a design space for dosage form manufacture has been developed to ensure delivery of desired clinical performance
- ❖ Critical process parameters have been linked to clinically relevant specifications (knowledge space)

Quality Risk Assessment

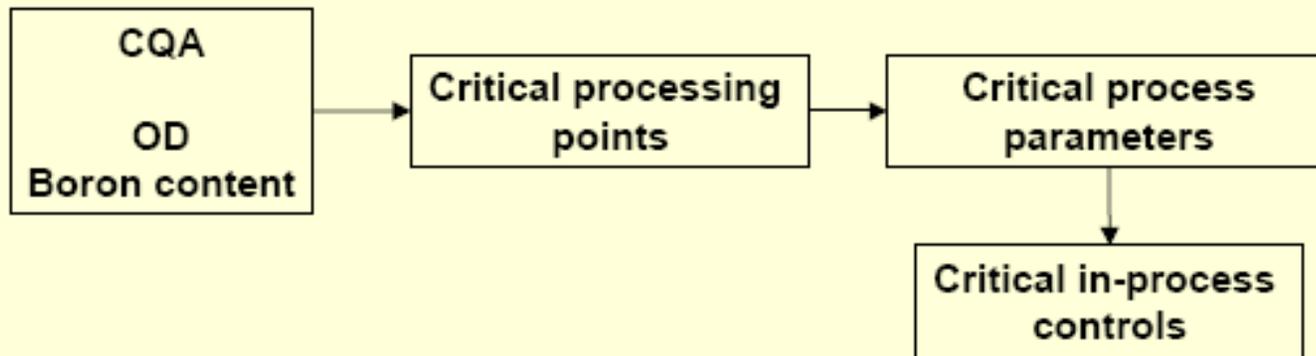
- ❖ Rating Probability: Occurrence of failure mode
- ❖ Rating Severity: Severity of effects of failure mode
- ❖ Rating Likelihood: Likelihood of detection of failure mode
- ❖ Pareto Chart: Relative importance of inputs

Product “x”

- ❖ NDA filing included a Pharmaceutical Development report per ICH Q8
- ❖ Comprehensive Quality Overall Summary (comp-QOS), to serve as the review document, was included in the filing
- ❖ Regulatory Agreement was also included in the filing
- ❖ Inclusion of PAT tools for control and real-time release is being pursued through a comparability protocol

Product “y” Methodology – CQA leads to Critical Points

- Critical processing points from
 - ▶ Knowledge of synthesis contributions
 - ▶ Processing experience related to scale production
 - ▶ Knowledge of physical attributes
 - ▶ Risk-based analysis of the API process



Product “y”

- ❖ CQA established for “y” drug substance used for intravenous formulations based on drug product performance
- ❖ Rigorous risk-based analysis carried out to determine the critical processing parameters for CQA
- ❖ Design space for crystallization established by using DoE

Product “y”

- ❖ In-process controls defined for each critical process parameter
- ❖ Process development involved use of PAT tools; opportunities for further implementation identified
- ❖ API development report to describe API process rationale and quality strategy (Comprehensive Quality Overall Summary)

FDA CMC Pilot Program Process

- ❖ The FDA Project manager plays a significant role in successful meeting interaction and coordination
 - Face-to-face meetings are held frequently
 - Telephone conferences are also scheduled
- ❖ Program requires a more interactive process between sponsor representative and the agency project manager

FDA CMC Pilot Program Process

❖ Benefits

- Close interaction with FDA ensures that complex scientific issues are handled in a proactive manner
- Discussion focused more on manufacturing science and product quality
- A successful QbD approach will provide a foundation to implement PAT and innovative technology sooner
- Enhanced coordination of Agency review by all disciplines

Interaction with EMEA PAT working group

- ❖ The meeting with EMEA PAT working group was productive
- ❖ The PAT working group provided constructive inputs
- ❖ Challenge: Interaction with assessors in EU is limited
- ❖ The regulatory advice from FDA and EMEA may differ in some areas

FDA CMC Pilot Program Process

❖ Challenges/Opportunities

- Quality by Design approach is not yet accepted globally, although there is extensive interest and support by Boards of Health
 - This will require preparation of traditional and QbD dossier modules
- Most firms have no previous experience in authoring a Comprehensive Quality Overall Summary to support QbD
 - Definition of contents to prevent repetition of information/material would streamline process
 - Lessons learned: Modular format is the best approach for life-cycle management
- CTD Format needs to be revisited for QbD filings

FDA CMC Pilot Program Process

❖ Challenges/Opportunities

- Comprehensive Quality Overall Summary and Regulatory Agreement are not globally acceptable approaches
- Regulatory agreement is a critical document and needs clarity for execution of post-approval strategy
- Expansion of design space during post-approval is a challenge

FDA CMC Pilot Program Process

❖ Challenges for FDA

- CMC pilot program may be time consuming for the FDA review and field inspection team
- In the short term this requires additional resources
- In the long term this will be balanced by the decrease in post-approval submissions.

FDA CMC Pilot Program Process

❖ Challenges for sponsor

- CMC pilot program may be time-consuming for the sponsor in the beginning
- Need to prepare Regional CTD documents
- The internal team needs to have expertise to answer complex regulatory, technical and compliance questions on evolving issues
- In the long term this will be balanced by the decrease in post-approval submissions

FDA CMC Pilot Program Process

❖ Challenges for Sponsor

- A culture shift is required on the part of the sponsor to fully engage in frequent pilot program interactions
 - Sponsors are used to extensive rehearsals to prepare for FDA meetings
 - More frequent interaction requires dynamic interaction and meeting participants who can “think on their feet” as well as generate trust between the Agency and Sponsor to facilitate scientific discussion

FDA CMC Pilot Program Process

❖ Conclusion

- CMC pilot program is an excellent mechanism for the sponsor to ensure alignment with the FDA on complex manufacturing issues
- Successful pilot program interactions requires a cultural shift for both the FDA and sponsor
- An internal working group with expertise in Quality by Design is critical for the success of QbD applications
- Further definition of the process and expectations will help streamline the submission process and success of the program/process

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