A New Pharmaceutical Quality Assessment System (PQAS) for the 21st Century – Why is it needed, what does it mean, and how do we get there?

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Outline

- CMC Submission and Review – Today’s Realities
- Pharmaceutical Quality Assessment System (PQAS)
  - What does it means
  - Key Elements
  - Implementation (Submissions, Assessment, Integration of review and inspection)
- CMC pilot program
- Regulatory Flexibility
- Conclusions
CMC Submission and Review – Today’s Realities

- My personal observations
  - Issues are common across 3 ICH regions
- Submissions
  - Focus more on data and format and less on critical analysis and scientific justification/rationale
  - Insufficient pharmaceutical development information
  - Contain voluminous data that not always scientific or not presented in a comprehensive manner
  - Concentrate mostly on chemistry and product specifications but less on manufacturing science
  - Apprehension on what to share with FDA
CMC Submission and Review – Today’s Realities

Review
- Resource intensive
- Need to search for relevant data in submission prior to analysis and critical assessment
- Guidance based
- Focuses on establishment of specifications

Regulatory Process
- Generally not friendly and communication not always timely
- Insufficient direct dialogue between FDA and applicant scientists
- Doesn’t allow for timely discussion and dispute resolution
- Lack of desired coordination and inconsistencies may exist among review divisions and field districts
CMC Submission and Review – Today’s Realities

- Today’s Regulatory Agreement
  - Applies to everything submitted in the application
  - Does not need to identify critical CMC elements (i.e. CQAs and CPPs) at time of approval
  - Results in:
    - Reluctance to share relevant scientific information with FDA
    - Many unnecessary supplements because every change could be considered “critical”
Current Challenges – Specifications (PQRI Specification Workshop)

- Empirical
  - Reliance on end product testing; not adequate to do real-time release
  - Tight AC to closely match clinical/stab batches in quality and consistency
  - No information on product design or process understanding
  - Limited data
    - Hindering statistical analysis
    - Leading to the need for supplements for post-approval material or process changes
Current Challenges - Process Validation

- Focuses primarily on the “3 batch” concept
  - Using the “best” – talent, day shift, same lot of raw materials, etc.
  - Is this representative of routine production operations?
  - Does this consistently ensure a “state of control”?
  - Sets up the mind set – “do not rock the boat” - the product is approved and its process validated!
- Continuous improvement is difficult
- Low efficiency is locked in!
Pharmaceutical Quality Assessment System (PQAS)

- Based on scientific knowledge and understanding of product and process by applying quality-by-design principles

Objective
  - To facilitate innovation and continuous improvement throughout the product lifecycle
  - To provide regulatory flexibility for specification setting and post-approval changes
  - To streamline the submission and review processes
PQAS - What does it mean?

- In a QbD paradigm, process understanding links manufacturing controls to CQAs/specifications and hence to the desired performance of the DP
- In the desired state, quality control is moved upstream to critical process steps and CPPs rather than relying on end-product testing
- To achieve this desired state, relevant design information is necessary for quality assessment
- It is imperative to define CQAs through multi-disciplinary interactions, e.g., clinical, pharm/tox
PQAS - Key Elements

- A more comprehensive Quality Overall Summary (QOS) and expanded PD section
- More relevant information on critical quality attributes and how they relate to clinical safety and effectiveness
- Critical steps and in-process controls identified and justified to demonstrate product knowledge and process understanding
- Significant sources of variability in manufacturing identified and controls to mitigate risk explained
- Less need for documentation of data not directly relevant to scientific evaluation of product quality
PQAS - Implementation

- Needs to be addressed and debated at the workshop
- What about currently marketed products?
- Culture change to address existing lack of understanding and trust
- Cost associated with implementing QbD in drug development
  - Business and marketing decisions
- Issues related to role and value of PD Information (Q8)
  - Required vs. “optional”
  - Reluctance to submit more information
  - “Application commitment”
  - May result in future regulatory burden (supplements/variations)
- A promising regulatory strategy - CMC Regulatory Agreement
Streamline the submissions

- No need to submit irrelevant, redundant, or unorganized data
- Need to submit relevant scientific information and analysis (summaries, tables and graphs)

PD Information

Comprehensive QOS, possibly as the “main” review document

Relevant product and manufacturing process design information
PQAS– Assessment (1)

- To ensure, through scientific assessment of applications, that necessary quality attributes are built in (QbD) and the drug product can be manufactured consistently with high quality for its intended use (i.e. safety and efficacy)

- CMC review is not:
  - Only about setting product specifications
  - Conducted in isolation (without clinical relevance)
  - To tell the applicant how to develop or manufacture its product
PQAS– Assessment (2)

- Assesses PD to understand how the applicant designed and developed its product and process
- Identifies CQAs (e.g., physical/chemical properties) of DP, DS, and excipients based on DP quality, performance, stability, and manufacturability requirements
  - Relates CQAs back to critical attributes of intermediates and in-process controls
  - Evaluates scientific rationale used to support the selection of CQAs and controls
PQAS– Assessment (3)

- Evaluates suitability of formulation
  - Evaluates impact of DS and excipient properties on DP quality, performance, manufacturability, and stability
  - Assesses justification provided by applicants for CQAs of DS, excipients and DP
  - Evaluates impact of container closure system and its components on DP quality, performance and stability
PQAS– Assessment of Manufacturing Process (1)

- Assesses appropriateness of process design
  - Evaluates scientific rationale used to support the selection of CPPs and in-process controls
  - Links material properties and critical steps to CQAs of DS, DP and intermediates
  - Assesses adequacy of relevant environmental controls, e.g., for moisture or oxygen sensitive formulation
PQAS– Assessment of Manufacturing Process (2)

- Evaluates appropriateness of in-process test acceptance criteria and CPP ranges
- Assesses suitability/capability of control methods
- Evaluates strategy for continuous improvement within the design space, if proposed in NDA submission
An Integrated Review-and-Inspection System (1)

- Office of New Drug Quality Assessment (ONDQA) assesses scientific basis of manufacturing process design and proposed manufacturing control strategy (MCS) in a risk-based paradigm.
- This assessment will be developed and shared with ORA investigators to facilitate a risk-based inspection.
- Equipment qualification, batch records will remain field’s responsibility.
- Post approval regulatory oversight of a MCS is a field responsibility with ONDQA technical input as needed.
An Integrated Review-and-Inspection System (2)

- CMC Pilot Program
  - Investigator is part of a review team (PAT Model)
  - During review, reviewer will communicate findings and share review with investigator
  - During PAI, investigator will share findings with reviewer
  - Joint PAI as needed
- If successful, adopt this system for most, if not all, applications based on established criteria
CMC Pilot Program

- Extension of program target dates
  - Request to participate - March 31, 2006
  - NDA submission – March 31, 2007

- Goals:
  - To implement PQAS
  - To evaluate elements of the new PQAS
  - To enable the public and industry to provide feedback to assist FDA in developing a guidance on the new quality assessment system
  - To establish appropriate metrics to evaluate quality of both submission and assessment

- At this stage, we do not expect full implementation of QbD principles in all manufacturing unit operations
Process of CMC Pilot Program

- Potential participants will discuss plans with ONDQA
- Once accepted, participants can meet with ONDQA as frequently as needed
- Assessment will be conducted, under the direct oversight of ONDQA Office Director, by a team of experienced scientists with good understanding of the new PQAS and strong background in PD and manufacturing processes
- Team Review
- Participation of ORA and CDER’s compliance
CMC Pilot Program - Observations

- FDA Focus
  - Public Health Protection
  - Good Science
  - Efficient process

- Strong interest in the pilot
  - Avenue to share information
  - Flexible review process

- Reluctance to challenge FDA’s regulatory system
  - Not gaining full benefits
  - Traditional proposals for specifications

- FDA is changing while industry is waiting!
Regulatory Flexibility

- Can be considered based on product and process understanding (QbD) in submission

- Pre-marketing:
  - Faster review
  - Higher probability for first cycle approval
  - Flexibility in setting specifications (within the design space)

- Post-marketing
  - Opportunities to update and/or modify the design space (e.g. comparability protocols)
  - Facilitates innovation and continuous improvement
  - Potential reduction and/or elimination of certain type of supplements
CMC Regulatory Agreement

- An agreement between FDA and applicant at the time of approval that
  - Lists of critical quality attributes and critical process parameters and their acceptance criteria and ranges
  - Define boundaries of design space
  - Describe manufacturing control strategy
  - Allow freedom to make changes within the design space by relying on manufacturer’s quality system and GMP controls
  - Can be updated and/or modified after approval

- Legal and implementation challenges
Conclusions

- FDA is moving forward with the implementation of PQAS
- FDA is striving for an international harmonized approach (ICH)
- FDA will continue to seek industry input and collaboration
- Regulatory flexibility is predicated on meaningful improvements to pharmaceutical development and scientific information submitted in application
- Today’s system may continue to exist
- Today’s challenges must be addressed
- Focus remains on availability of safe, effective and high quality pharmaceuticals