

Pharmaceutical Quality Assessment System (PQAS) in the 21st Century

Moheb M. Nasr, Ph.D.

CDER, FDA

MOHEB.NASR@FDA.HHS.GOV

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Outline

- FDA's GMPs for the 21st Century Initiative
- Challenges in traditional CMC program
- Pharmaceutical Quality Assessment System (PQAS) in the 21st Century
 - What is Quality by Design (QbD)
 - Submission and assessment under PQAS
- Where are we today?
 - Pre-Marketing Review
 - Risk-Based Post-Marketing Evaluation
- Benefits and regulatory flexibility
- Conclusions



FDA's GMPs for the 21st Century Initiative, September 2004 Report

- Establishment of a Council on Pharmaceutical Quality
- Development of several science-based guidances, policies and training programs
- Development of a Quality Systems Guidance
- Implementation of risk-based management Plan
- Establishment of PQAS

Challenges in Traditional CMC Program



■ Submissions

■ Focus

- More on data and format
- Based on prescriptive regulatory guidances and traditional industry practices
- Less on critical analysis and scientific justification/rationale

■ Data

- Voluminous
- Not always presented in a concise and organized manner

Challenges in Traditional CMC Program



- Submissions
 - Pharmaceutical Development Information
 - Insufficient to show understanding
 - Concentration
 - Mostly on chemistry and product specifications
 - Less on manufacturing process
 - Reflect apprehension on what to share with FDA



Challenges in Traditional CMC Program

- Review
 - Data mining prior to analysis and critical assessment
 - Focuses on establishment of specifications
- Regulatory Process
 - Communication not always timely and lacks direct dialogue between FDA and applicant scientists
 - Inconsistencies and lack of desired coordination may exist among review divisions and field districts



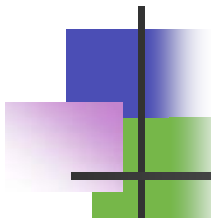
Challenges in Traditional CMC Program

- When NDA is approved
 - There is no need to identify critical CMC elements (i.e. CQAs and CPPs) at time of approval
 - Everything submitted in the application is locked in
- The consequences are:
 - Reluctance to share relevant scientific information with FDA
 - Many unnecessary supplements because every change could be considered “critical”
 - Focus on “Process Validation” and not on “Process Understanding”




Challenges in Traditional CMC Program

- Process Validation
 - Focuses primarily on reproducibility rather than robustness
 - Typically 3 consecutive batches
 - Usually same lots of raw materials, same operators, etc.
 - Validation “freezes” the process
 - Most process improvement requires regulatory approval or notification
 - Low efficiency is locked in!



Pharmaceutical Quality Assessment System (PQAS) in the 21st Century

- FDA is implementing the Pharmaceutical Quality Assessment System (PQAS) in the 21st Century Initiative
- PQAS promotes the science and risk-based approach to regulation as described in the Pharmaceutical Quality Initiative for the 21st Century
- PQAS Initiative applies to new drugs, including biotech products
- PQAS was established to encourage the pharmaceutical industry to apply quality-by- design (QbD) principles to drug development



Pharmaceutical Quality Assessment System (PQAS) - Elements

- Submission of knowledge-rich, scientific information that demonstrates product and process understanding
- Robust manufacturing processes designed and controlled to reproducibly deliver quality product
- Consistency in FDA's regulatory approach to assessment of new drugs
- Setting of appropriate specifications based on desired product performance, safety and clinical relevance
- Innovation and continuous improvement facilitated throughout product life cycle
- Regulatory flexibility based on enhanced product knowledge and process understanding



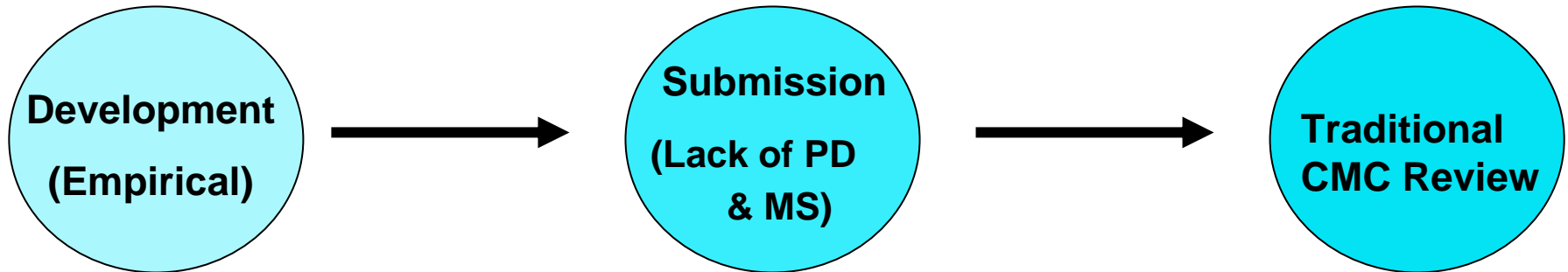
Current System vs. Desired State

Traditional CMC Submission	Desired State – PQAS
Quality by Testing and Inspection	Quality by Design – quality assured by well designed product & process
Data intensive application – disjointed information without “big picture”	Knowledge rich submission – supporting product & process design
Specifications based on process history	Specifications based on product performance requirements
“Frozen process” discouraging changes	Flexible process within design space allowing continuous improvement
Focus on reproducibility – often avoiding or ignoring variation	Focus on robustness – understanding and controlling variation

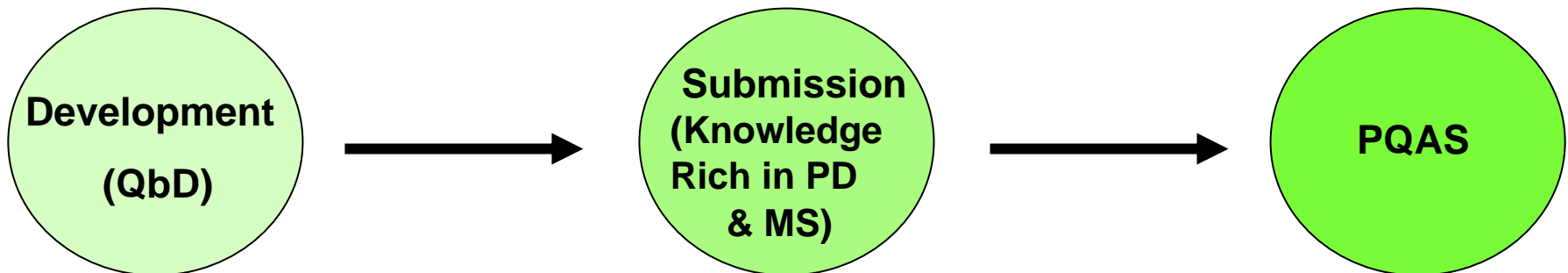


Current System vs. Desired State

Current System



Desired State

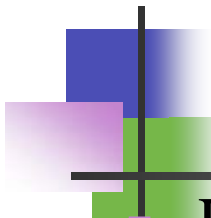




What is Quality by Design (QbD)?

- **In a Quality-by-Design system:**
 - The product is designed to meet patient needs and performance requirements
 - The process is designed to consistently meet product critical quality attributes
 - The impact of starting raw materials and process parameters on product quality is understood
 - Critical sources of process variability are identified and controlled
 - The process is continually monitored and updated to allow for consistent quality over time





Pharmaceutical Quality Assessment System (PQAS) - Implementation

- Restructuring ONDC – Completed in November 2005
- Transfer of drug release assessment functions – Completed in April 2006 - Will be addressed at this DIA meeting
- Withdrawals of prescriptive and outdated guidances – June 2006
 - Development of new guidances– ongoing
- ICH Quality Initiatives (Q8, 9 & 10, QOS, DS, etc.) – Will be addressed at this DIA meeting
- CMC Pilot Program (focus on enhanced PD and QbD) – ongoing
- CMC Agreement – ongoing
- CMC Dispute resolution process– ongoing
- Implementation of a modern quality management system – ongoing



PQAS – Submissions

- Streamlined submissions
 - Need to submit relevant scientific information and analysis (e.g., summaries, tables and graphs)
- Expanded pharmaceutical development information
- Comprehensive QOS, possibly as the “main” review document
 - ICH Discussions in Chicago and Yokohama
 - Will be addressed at this DIA meeting
- Relevant product and manufacturing process design information
- Applicants’ assessment/analysis included in submission



PQAS – Assessment

- To ensure 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:
 - Data audit or mining
 - Only about setting product specifications
 - Conducted in isolation (without clinical relevance)
 - To tell the applicant how to develop or manufacture its product



PQAS – Assessment

- Assesses PD to understand how the applicant designed and developed its product and process
- Evaluates proposed CQAs (e.g., physical/chemical properties) of DP, DS, and excipients based on DP quality, performance, stability, and manufacturability requirements
- Evaluates suitability of formulation
- 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



Where are we today?

- CMC reviews completed (FY 2005)
 - 186 NDAs, 919 INDs, and 1754 supplements
- Move to White Oak, October 2005
- CMC Workshop, October 2005
- New review process, November 2005
- CMC Pilot, ongoing, first approval May 2006
- Training and recruiting efforts, ongoing
- FDA Quality Initiatives Workshop, Feb. 28, 2007



Pre-marketing Review

- Enhanced communication with OND
- Initial Quality Assessment (IQA)
- Team review
- Peer review as an element of QA program
- CMC only meetings
 - Provided wherever needed, in addition to multi-disciplinary EOP2, pre-NDA, etc., meetings
 - Not intended to discuss CMC issues in isolation; other disciplines often invited



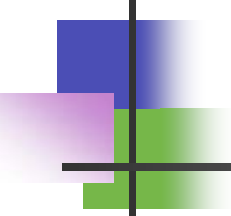
Post-marketing Evaluation - Mission

- Foster implementation of continuous improvement, innovation and effective manufacturing changes within a process knowledge framework
- Develop a streamlined review process within a risk-based framework, and capture knowledge from evaluation and review
- Develop strategies to streamline review process and to downgrade or eliminate certain types of supplements based upon risk based analysis



Post-marketing Evaluation - Risk-Based Quality Assessment

- Approaches to assigning risk categories
 - Impact of proposed change on product performance
 - Degree of understanding of product design, desired product performance and manufacturing process
- Supplement triage to identify degree of risk
 - Will be addressed at this DIA meeting



Pharmaceutical Quality Assessment System (PQAS) - Benefits

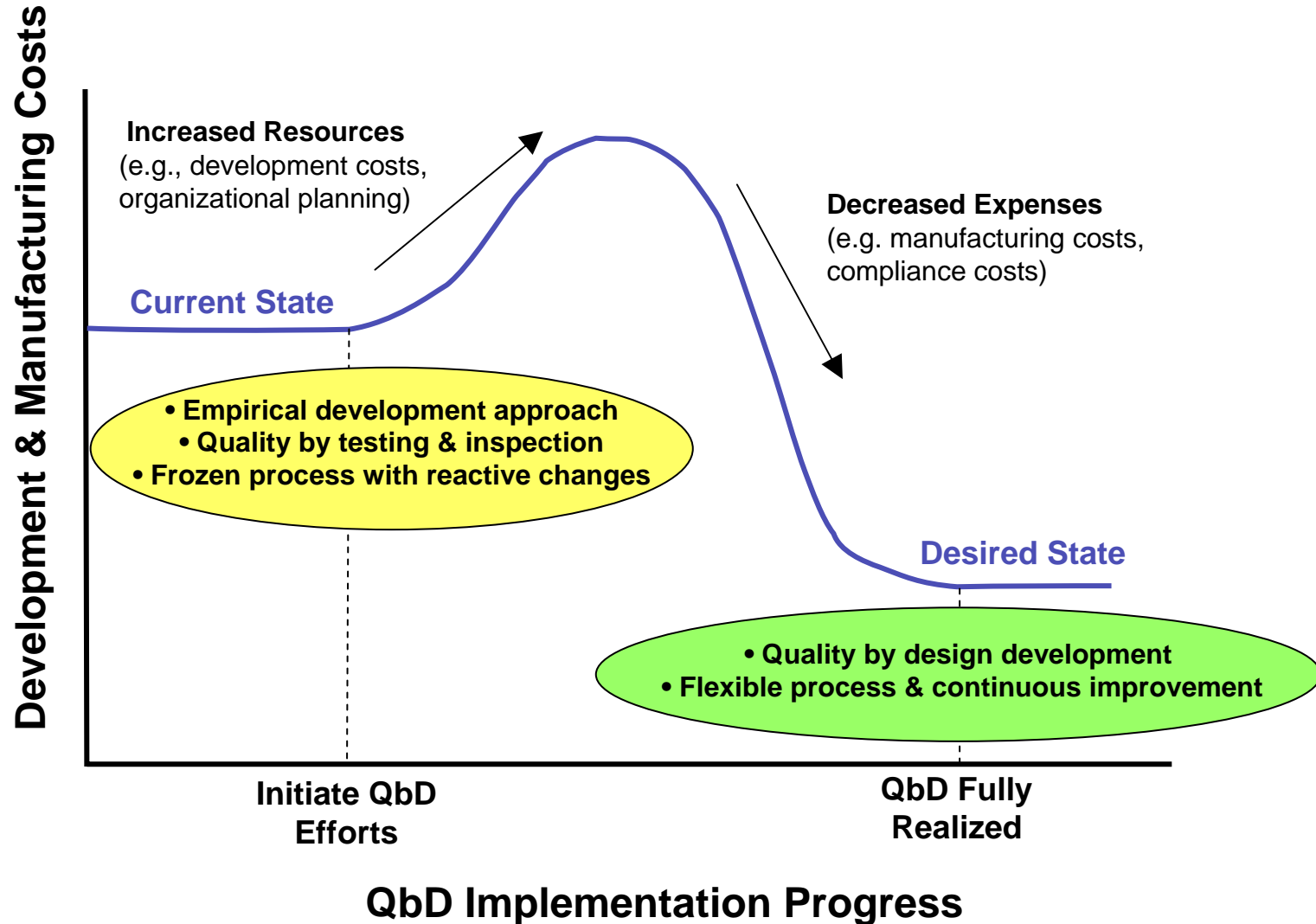
- Innovation and continuous improvement facilitated throughout the product lifecycle
- Better product/process understanding is likely to deliver a more robust and efficient process
- Efficient and effective review process
 - Higher probability for first cycle approval
- Regulatory flexibility based upon enhanced product and process knowledge



Regulatory Flexibility

- Predicated on demonstrated product knowledge and process understanding
- Opportunities:
 - Flexibility in setting specifications/acceptance criteria
 - Elimination of certain traditionally required end-product testing
 - Elimination of certain type of post-marketing supplements
 - Opportunities for real time release (RTR)

Cost and Benefit of QbD





Conclusions

- **The current system is adequate for regulatory submission**
 - Quality is assured by testing and inspection
 - Considerable regulatory oversight
- **However, QbD is the desired approach**
 - QbD principles should result in a higher level of assurance of product quality
 - Additional product and process understanding may result in regulatory flexibility
- **Focus remains on availability of safe, effective and high quality pharmaceuticals**