

# Pharmaceutical Quality Assessment System (PQAS) in the 21<sup>st</sup> Century

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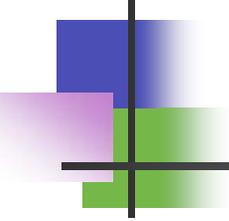
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DIA Annual Meeting

Philadelphia, PA

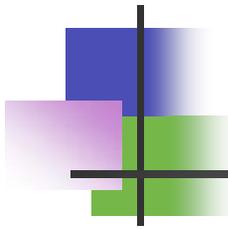
June 19, 2006



# Outline

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- FDA's GMPs for the 21<sup>st</sup> Century Initiative
- Challenges in traditional CMC program
- Pharmaceutical Quality Assessment System (PQAS) in the 21<sup>st</sup> 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

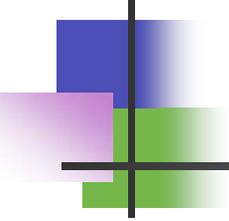


# FDA's GMPs for the 21<sup>st</sup> Century Initiative, September 2004 Report

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- 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



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- Submissions

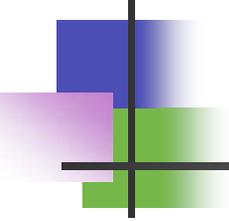
- Focus

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

- Data

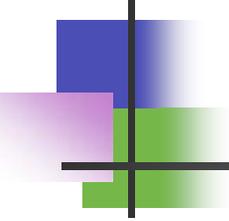
- Voluminous
    - Not always presented in a concise and organized manner

# Challenges in Traditional CMC Program



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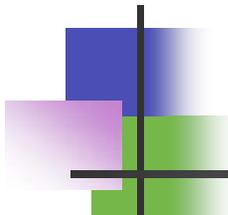
- Submissions
  - Pharmaceutical Development Information
    - Insufficient to show understanding
  - Concentration
    - Mostly on chemistry and product specifications
    - Less on manufacturing process
  - Reflect apprehension on what to share with FDA



# Challenges in Traditional CMC Program

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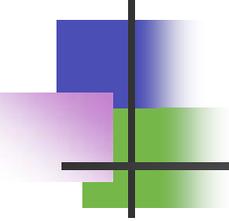
- Review
  - Data mining prior to analysis and critical assessment
  - Focuses on establishment of specifications
- Regulatory Process
  - Communication not always timely and lacks direct dialogue between FDA and applicant scientists
  - Inconsistencies and lack of desired coordination may exist among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



# Challenges in Traditional CMC Program

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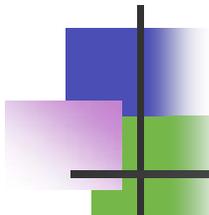
- When NDA is approved
  - There is no need to identify critical CMC elements (i.e. CQAs and CPPs) at time of approval
  - Everything submitted in the application is locked in
- The consequences are:
  - Reluctance to share relevant scientific information with FDA
  - Many unnecessary supplements because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



# Challenges in Traditional CMC Program

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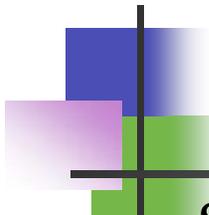
- Process Validation
  - Focuses primarily on reproducibility rather than robustness
  - Typically 3 consecutive batches
    - Usually same lots of raw materials, same operators, etc.
  - Validation “freezes” the process
  - Most process improvement requires regulatory approval or notification
  - Low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



# Pharmaceutical Quality Assessment System (PQAS) in the 21<sup>st</sup> Century

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- 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



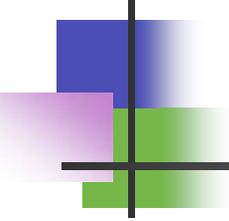
# Pharmaceutical Quality Assessment System (PQAS) - Elements

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- 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

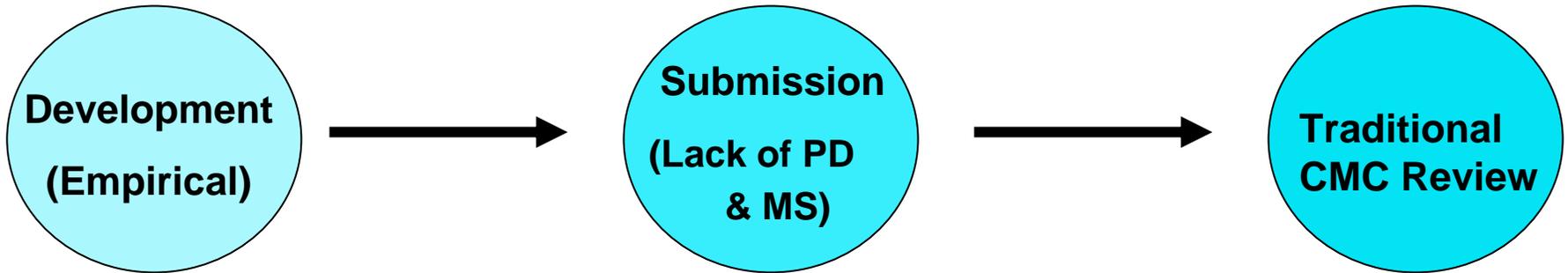
<b>Traditional CMC Submission</b>	<b>Desired State – PQAS</b>
Quality by Testing and Inspection	Quality by Design – quality assured by well designed product & process
Data intensive application – disjointed information without “big picture”	Knowledge rich submission – supporting product & process design
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

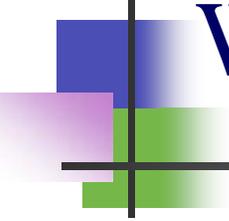
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## Current System



## Desired State



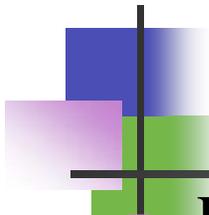


# What is Quality by Design (QbD)?

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- **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

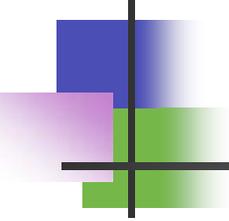




# Pharmaceutical Quality Assessment System (PQAS) - Implementation

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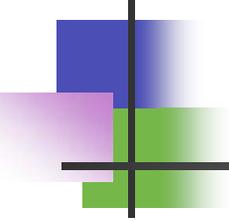
- Restructuring ONDC – Completed in November 2005
- Transfer of drug release assessment functions – Completed in April 2006 - Will be addressed at this DIA meeting
- Withdrawals of prescriptive and outdated guidances – June 2006
  - Development of new guidances– ongoing
- ICH Quality Initiatives (Q8, 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

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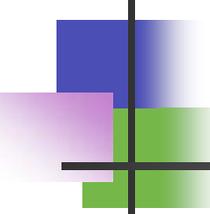
- Streamlined submissions
  - Need to submit relevant scientific information and analysis (e.g., summaries, tables and graphs)
- Expanded pharmaceutical development information
- Comprehensive QOS, possibly as the “main” review document
  - ICH Discussions in Chicago and Yokohama
  - Will be addressed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



# PQAS – Assessment

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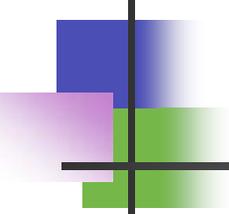
- To ensure that necessary quality attributes are built in (QbD) and the drug product can be manufactured consistently with high quality for its intended use (i.e. safety and efficacy)
- CMC review is not:
  - Data audit or mining
  - Only about setting product specifications
  - Conducted in isolation (without clinical relevance)
  - To tell the applicant how to develop or manufacture its product



# PQAS – Assessment

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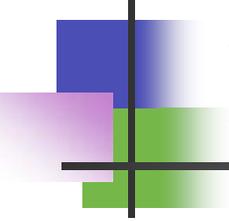
- Assesses PD to understand how the applicant designed and developed its product and process
- Evaluates proposed CQAs (e.g., physical/chemical properties) of DP, DS, and excipients based on DP quality, performance, stability, and manufacturability requirements
- Evaluates suitability of formulation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

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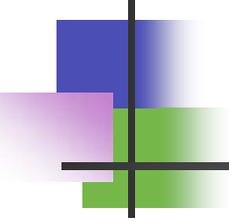
- CMC reviews completed (FY 2005)
  - 186 NDAs, 919 INDs, and 1754 supplements
- Move to White Oak, October 2005
- CMC Workshop, October 2005
- New review process, November 2005
- CMC Pilot, ongoing, first approval May 2006
- Training and recruiting efforts, ongoing
- FDA Quality Initiatives Workshop,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



# Pre-marketing Review

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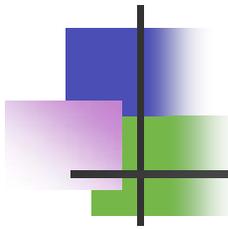
- Enhanced communication with OND
- Initial Quality Assessment (IQA)
- Team review
- Peer review as an element of QA program
- CMC only meetings
  - Provided wherever needed, in addition to multi-disciplinary EOP2, pre-NDA, etc., meetings
  - Not intended to discuss CMC issues in isolation; other disciplines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



# Post-marketing Evaluation - Mission

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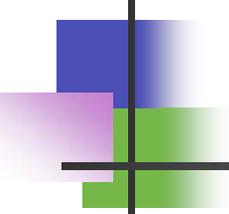
- Foster implementation of continuous improvement, innovation and effective manufacturing changes within a process knowledge framework
- Develop a streamlined review process within a risk-based framework, and capture knowledge from evaluation and review
- Develop strategies to streamline review process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



# Post-marketing Evaluation - Risk-Based Quality Assessment

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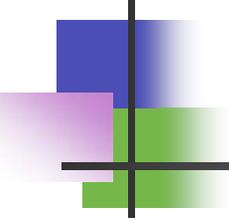
- Approaches to assigning risk categories
  - Impact of proposed change on product performance
  - Degree of understanding of product design, desired product performance and manufacturing process
- Supplement triage to identify degree of risk
  - Will be addressed at this DIA meeting



# Pharmaceutical Quality Assessment System (PQAS) - Benefits

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- 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



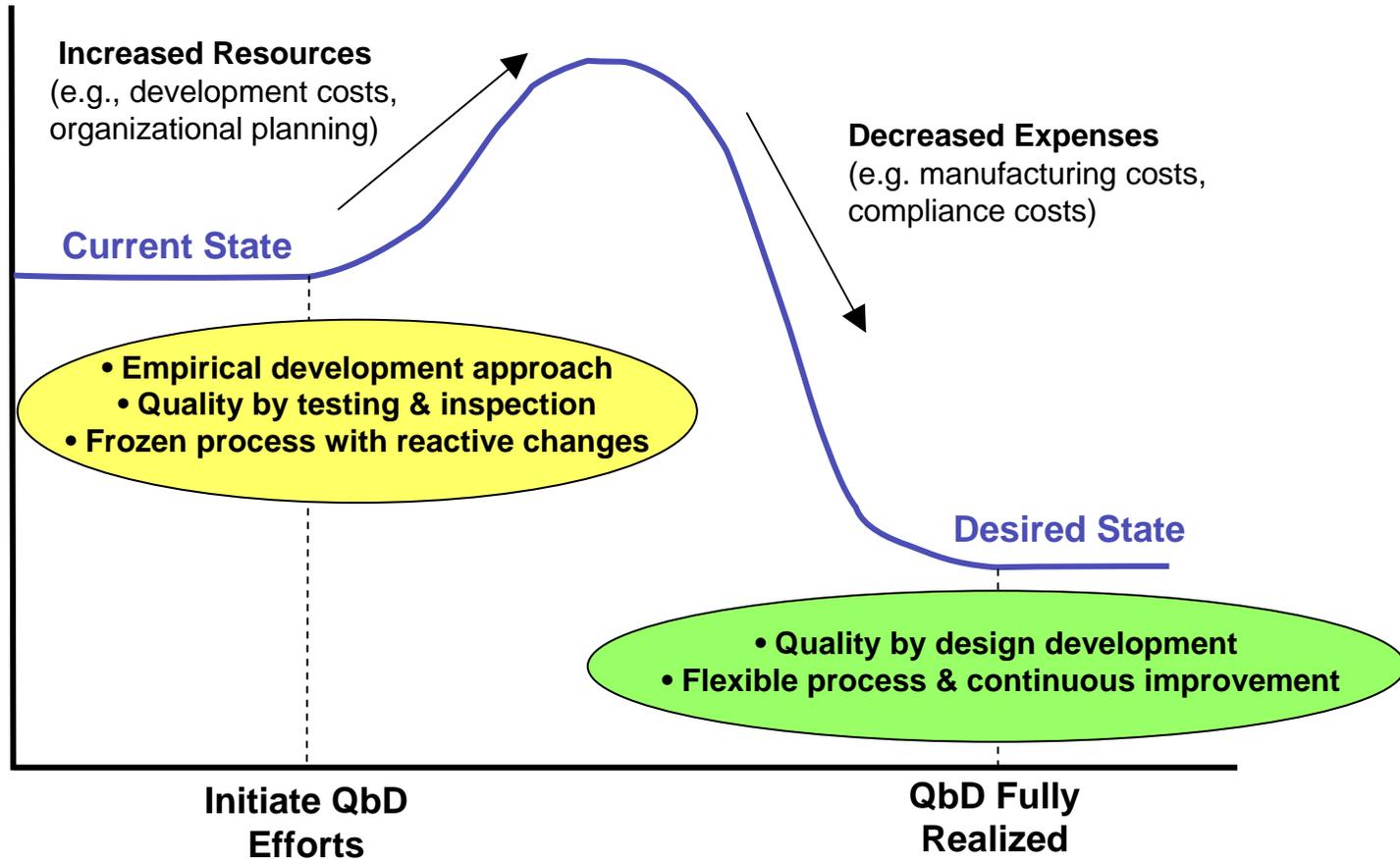
# Regulatory Flexibility

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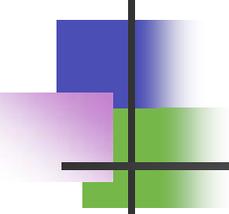
- Predicated on demonstrated product knowledge and process understanding
- Opportunities:
  - Flexibility in setting specifications/acceptance criteria
  - Elimination of certain traditionally required end-product testing
  - Elimination of certain type of post-marketing supplements
  - Opportunities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

# Cost and Benefit of QbD

Development & Manufacturing Costs



QbD Implementation Progress



# Conclusions

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- **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**