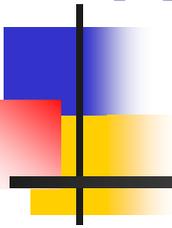
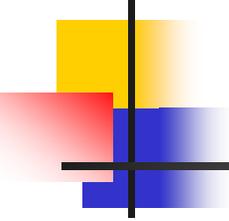


CMC and GMP Track, Topic 1
DIA Annual Meeting, Philadelphia, PA, June 19-22, 2006



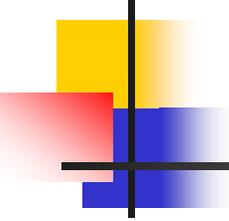
The ONDQA CMC Pilot Program - an FDA Perspective

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Office of Pharmaceutical Science
Center for Drug Evaluation and Research
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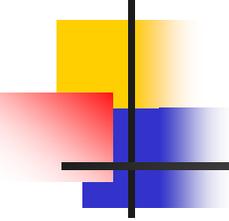
Outline

- Drivers: Q8; QbD; PAT; PQAS
- Objectives of Pilot Program
- Process of Pilot Program
 - Program timeline/goal/status; participation process; submission criteria; review process
- Observation and evaluation of submissions under Pilot Program to date
 - CQOS; expanded P.2; application of QbD; CQAs and CPPs; design space; regulatory flexibility; CMC regulatory agreement
- Benefits and challenges of Pilot Program
- Summary



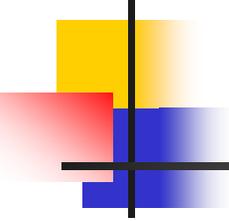
Q8 - Design Space

- Definition: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality
- Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process.
- Design space is proposed by the applicant and is subject to regulatory assessment and approval



Q8 - Regulatory Flexibility

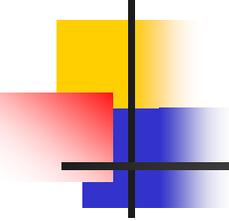
- Proposed by applicant, and approved by regulator, based on demonstrated product knowledge and process understanding
- Degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided
- Opportunities to facilitate
 - risk-based regulatory decisions (reviews and inspections)
 - manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review
 - reduction of post-approval submissions
 - real-time quality control, leading to a reduction of end-product release testing



FDA's view on Quality by Design (QbD)

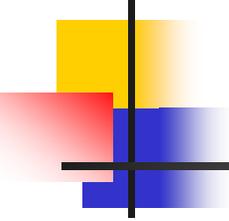
- In a Quality-by-Design system:
 - The product is designed to meet performance requirements
 - The process is designed to consistently meet product critical quality attributes
 - The impact of formulation components and process parameters on product quality is understood
 - Critical sources of process variability are identified and controlled
 - The process is continually monitored and updated to assure consistent quality over time





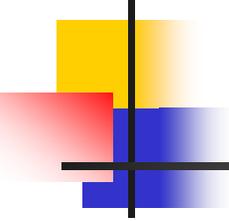
FDA's View on QbD

- The CMC information currently required in an NDA is adequate to support approval in the U.S.
- 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
- QbD is full understanding of product and process as they relate to product performance
 - QbD is more than process and formulation optimization
 - QbD is more than justification of CQAs and CPPs
 - This may be an iterative/continuous process



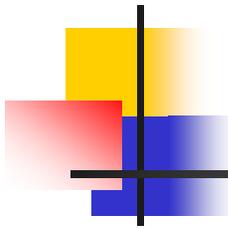
Pharmaceutical Quality Assessment System

- PQAS is ONDQA's new science- and risk-based approach to CMC review that
 - Emphasizes submissions rich in scientific information demonstrating product knowledge and process understanding
 - Focuses on critical pharmaceutical quality attributes and their relevance to safety and effectiveness
 - Enables FDA to provide regulatory flexibility for specification setting and post-approval changes
 - Facilitates innovation and continuous improvement throughout product lifecycle



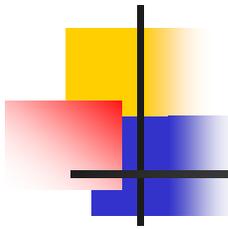
Pilot Program Objectives

- To provide participating firms an opportunity to submit CMC information demonstrating
 - application of quality-by-design (QbD) principles
 - product knowledge and process understanding
- To enable FDA to evaluate
 - CQOS; new concepts and approaches in Q8 and PAT Guidance; QbD; CMC Agreement; team review
- To enable FDA to seek public input in developing a guidance on the new PQAS



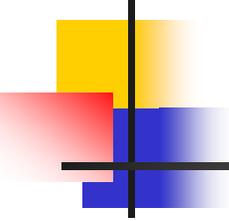
Pilot Program Timeline, Goal, and Status

- Program timeline
 - Original FR Notice re CMC Pilot: July 14, 2005
 - 2nd FR Notice to extend deadlines: September 19, 2005
 - Deadline to request for participation: March 31, 2006
 - Deadline to submit NDA or supplement: March 31, 2007
- Goal: 12 original NDAs and supplements
- Status
 - Goal may be met, including supplement(s)
 - Some have been submitted and are under review
 - One has been approved
 - Others are to be submitted within a year



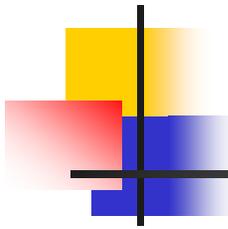
Participation Process

- Interested applicant submits to the Docket [No. 2005N–0262] a written request to participate
- Applicant meets with FDA to discuss its plan at a high level and a rationale for participation
- FDA determines acceptability based on whether submission criteria are met
- If s/NDA is accepted, ONDQA forms a review team and meets with applicant before NDA is submitted
- Once s/NDA is submitted, applicant meets with FDA as frequently as needed



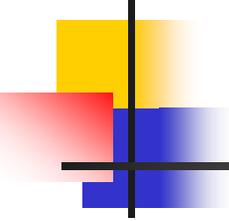
Submission Criteria

- An expanded Pharmaceutical Development (P.2)
- More relevant scientific information
 - Demonstrating QbD, product knowledge, and process understanding
 - Identifying critical quality attributes and how they relate to safety and effectiveness
 - Linking material attributes and process parameters to quality attributes
 - Identifying possible sources of variability and how associated risks can be mitigated
 - Describing process controls and quality assurance strategies
- A comprehensive Quality Overall Summary (CQOS)



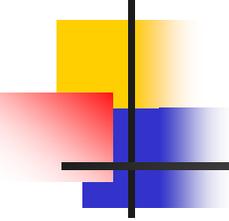
Review Process

- CMC assessment performed by a team of experienced reviewers with
 - good understanding of the new PQAS, and
 - strong background in pharmaceutical and manufacturing sciences
- Process managed and overseen by ONDQA IO with PM support
- Integrated review/inspection team
- Frequent meetings with applicant before submission, during review, and after approval



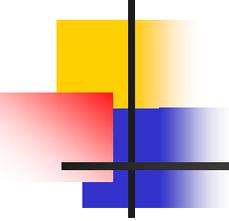
Comprehensive QOS

- CQOS's in pilot NDAs observed to date
 - All were formatted according to, and with links to, Module 3 of CTD-Q
 - Some were concise summaries of Module 3
 - some were so detailed that they were nearly identical to Module 3
- Review teams' evaluation to date
 - A concise version can be a good starting point for review
 - Detailed CQOS identical to Module 3 does not add value
 - Applicant's own assessment and conclusions are useful
 - A brief, succinct overview of QbD could be very useful



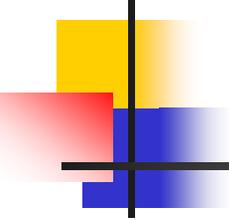
Expanded PD (P.2)

- Observed to date:
 - 3.2.S.2.6 in certain pilot NDAs provided more process understanding information in DS than in typical NDAs
 - 3.2.P.2 in all pilot NDAs provided more scientific information than typical NDAs regarding DP
 - formulation and product development
 - process understanding and optimization
- Review teams' evaluation:
 - Most demonstrated process reproducibility, but not necessarily process robustness
 - The more relevant scientific information is useful in facilitating CMC review and justifying proposed regulatory flexibility



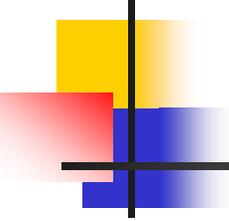
Application of QbD

- All pilot NDAs to date contained some elements of QbD:
 - Critical quality attributes (CQAs)
 - Formulation development
 - Risk assessment; design of experiments
 - Impact of DS/excipient properties on DP manufacturability and/or CQAs
 - Process development; impact of process parameters on CQAs
 - Design space for critical DS/excipient attributes and CPPs
- Other observations:
 - Process reproducibility, but not necessarily process robustness, demonstrated
 - Process analyzers used to collect data in development, but not for commercial production



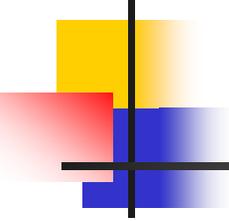
CQAs and CPPs

- The following were identified/justified or differentiated in some, but not all, pilot NDAs to date:
 - CQAs for DS (drug substance), DP (drug product), and, as appropriate, intermediates
 - CPPs (critical process parameters) for DS and DP manufacturing processes
 - Linkage between CPPs and CQAs
 - CPPs vs non-CPPs
 - Design space vs control space for CPPs and for non-CPPs



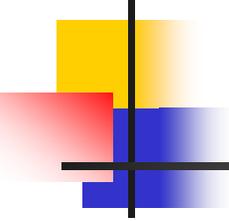
Design Space

- Issues raised:
 - How were design space and control space established for each unit operation?
 - Is the design space for each unit operation independent of equipment design and batch size?
 - How does control space relate to design space?
 - How does control space relate to operational ranges in the Master Batch Record?



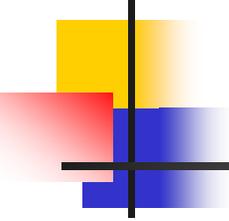
Design Space (2)

- Where, and how, can process knowledge and design space information be captured at an operational level in the submission? One suggestion is to capture in 3.2.P.3.3, Manufacturing Process Description, the following:
 - Information on design space, in addition to initial operating ranges typically included in 3.2.P.3.3
 - CPPs and non-CPPs differentiated
 - Process understanding information, gained from development and optimization studies, e.g.,
 - impact of process parameters on CQAs
 - parameters found not to influence any CQAs within the ranges studied



Regulatory Flexibility

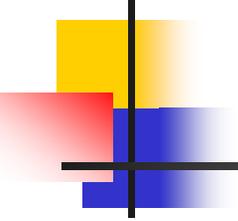
- Examples of proposed regulatory flexibility:
 - In-process testing in lieu of end-product testing, e.g., blend uniformity in lieu of content uniformity
 - Real-time release in lieu of end-product testing
 - Annual report for post-approval changes within established design space
- Degree of flexibility granted would depend on level of knowledge and understanding demonstrated



Post-Approval Design Space Changes

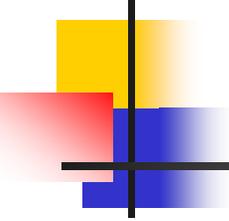
Issues raised:

- How will the design space be reassessed, verified, or redefined when a change is made in a unit operation, process parameters, in-process controls, or when a new piece of equipment is introduced?
- What is the regulatory strategy for managing changes in design space, including expanding and contracting the design space, for critical and non-critical parameters?



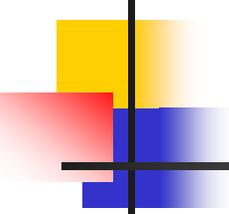
CMC Regulatory Agreement

- An agreement between FDA and applicant which
 - Identifies CQAs and CPPs, and describes control strategies
 - Describes established design space for material and process
 - Describes how changes to CQAs and CPPs will be managed and assessed
 - Describes how design space will be reassessed, verified, or redefined
 - when a change is made in a unit operation, process parameters, in-process controls, or
 - when a new piece of equipment is introduced
 - Describes the regulatory strategy for managing changes in (including expansion of) design space



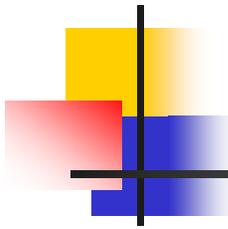
Review Management

- ONDQA reorganization made Pilot feasible
 - Team review; Manufacturing Science staff; Project Management staff
- Frequent communications with applicant
- Integrated review/inspection team
 - Frequent dialog with Compliance and Field before submission and during review
 - Sharing of review findings with investigator
 - Joint PAI between reviewer and investigator
- QbD-related issues would not hold up NDA approval



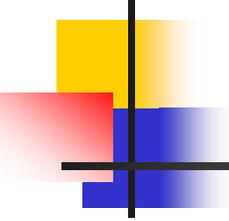
Benefits

- Pilot enables industry and FDA to
 - explore ways to implement Q8, PAT, and PQAS
- Pilot enables FDA to
 - better define what constitutes a QbD-based submission
 - better define what constitutes a science-based risk assessment
 - use experience gained to develop a guidance on QbD and PQAS
- Good science leads to better quality product, fewer product rejects/recalls, and enhanced public health protection



Challenges

- Level of detail in submission demonstrating product knowledge and process understanding
- Expectations for a QbD-based submission while addressing traditional requirements
- Providing regulatory flexibility while assuring product quality
- Industry's continuous apprehension in sharing information, including failed experiments, with FDA
- Cultural changes needed in industry and FDA
- More resources needed initially for industry & FDA



Summary

- Pilot Program got off to a good start in meeting its initial goal for industry participation
- Aspects of QbD were included in Pilot NDAs, and expanded PD is useful
- CQOS needs further development
- Scientific approaches to CQAs, CPPs, & design space need further development
- Regulatory flexibility is being proposed
- CMC Regulatory Agreement is being explored
- Program benefits FDA in developing guidance to implement QbD and PQAS
- Challenges remain for industry and FDA