



What Does Quality By Design Bring To Your Drug Development Program?

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Sarah Pope Miksinski, Ph.D.

Branch Chief (Chemistry, Manufacturing and Controls)

Branch 5/Division of Pre-Marketing Assessment 3

Office of New Drug Quality Assessment



Outline

- Quality
- Quality by Design (QbD)
- QbD approach
 - Product profile
 - Critical quality attributes (CQAs)
 - Risk management
 - Design space
- Effect on clinical trials/when to do QbD
- Accelerating drug development - considerations



What is Quality?

- The degree to which a set of inherent properties of a product, system, or process fulfills requirements (ICH Q9)
- The suitability of either a drug substance or drug product for its intended use. Includes such attributes as the identity, strength, and purity (ICH Q6A)

ICH Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.

ICH Q9 Quality Risk Management



Why is Quality Important?

- Ties product performance to label claim
- Applies to design, manufacture and clinical use of product
- Relates critical attributes of the drug to patient safety and fitness for use
- Necessary for product availability to patient (i.e., poor quality often results in recalls and shortages)



What is Quality by Design?

Systematic approach to development

- Begins with predefined objectives
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management

From ICH Q8(R1)

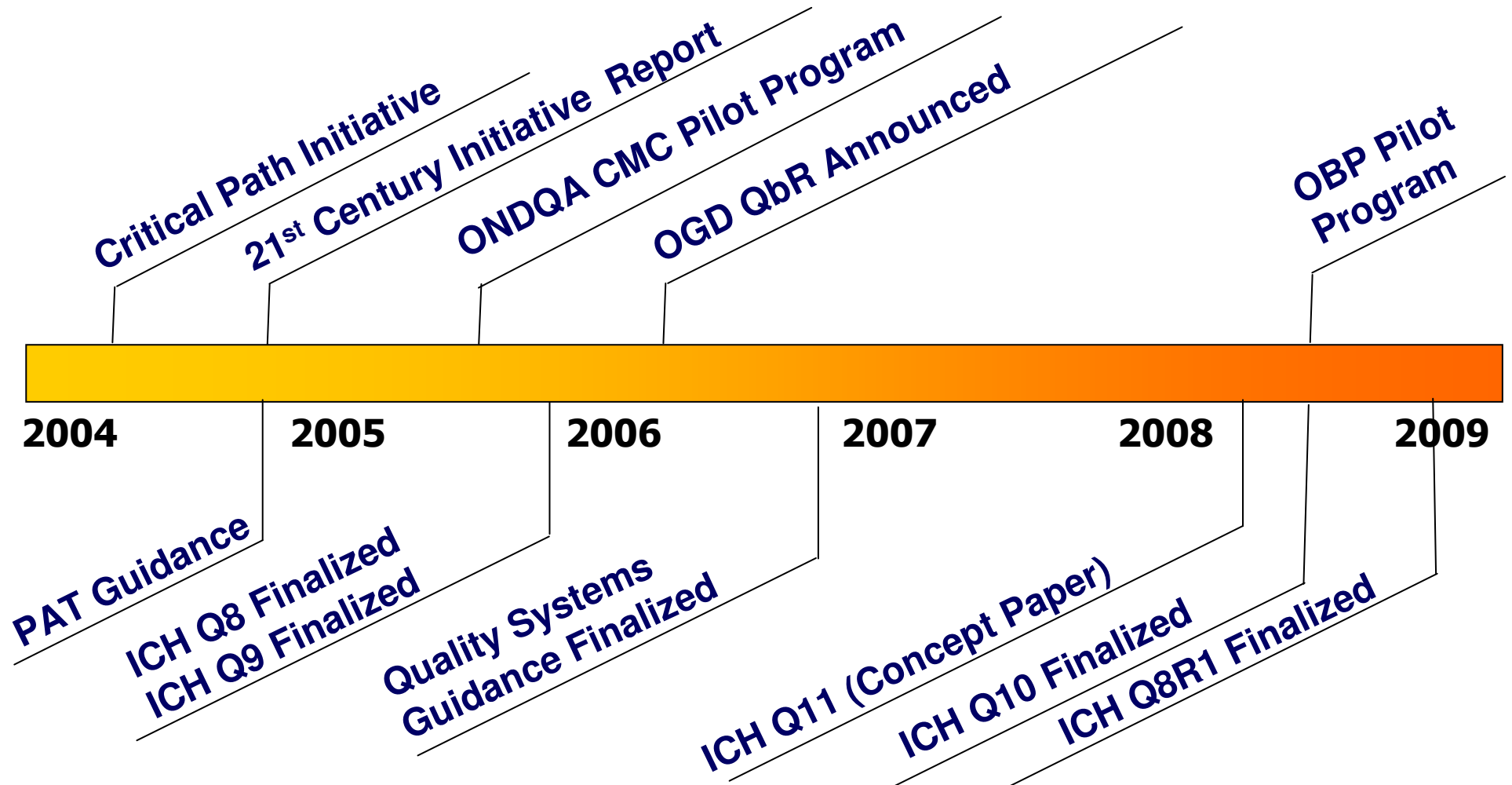


Why QbD?

- Higher level of assurance of product quality
- Cost saving and efficiency for industry
 - Facilitate innovation to address unmet medical needs
 - Increase efficiency of manufacturing process and reduce manufacturing cost and product rejects
 - Minimize/eliminate potential compliance actions, costly penalties and recalls
 - Opportunities for continual improvement
- More efficient regulatory oversight
 - Enhance opportunities for first cycle approval
 - Streamline post approval manufacturing changes and regulatory processes
 - More focused PAI and post approval cGMP inspections

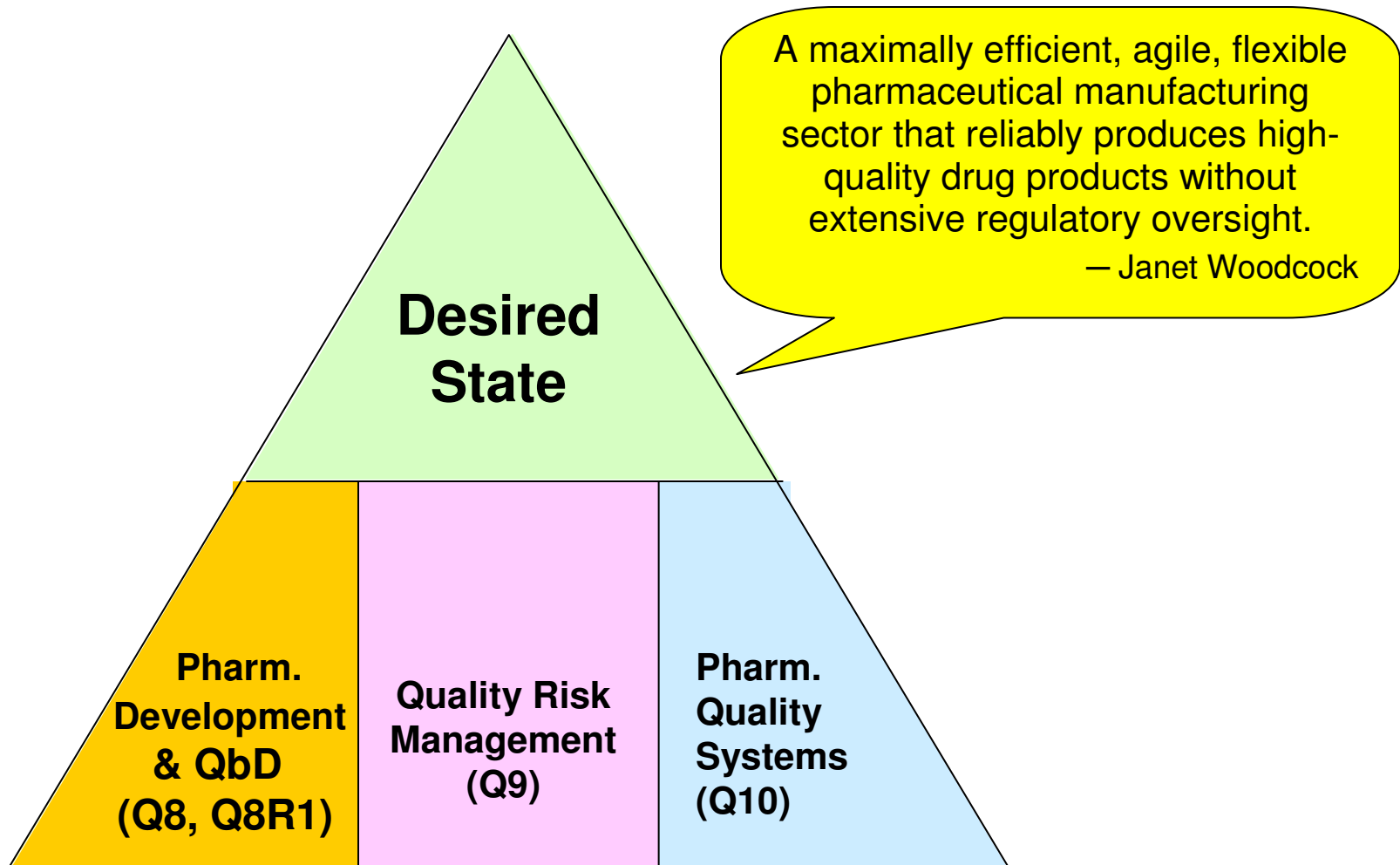


FDA Initiatives: A Quality Timeline





The Desired State



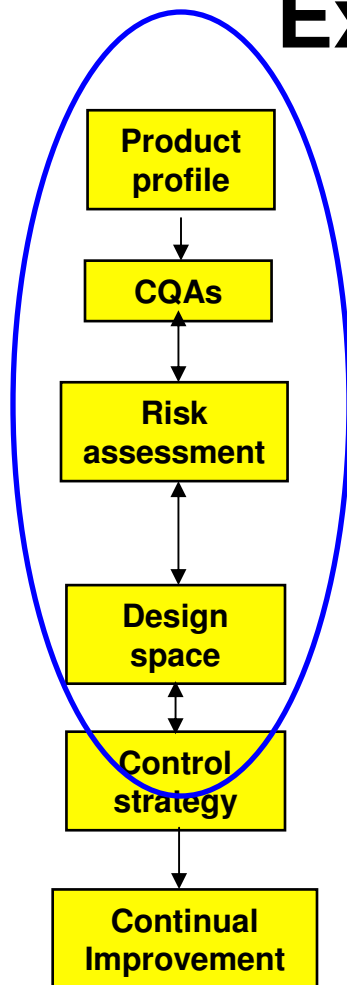


Characteristics of Desired State

- Manufacturers have extensive knowledge about critical product and process parameters and quality attributes
- Manufacturers control process through quality systems over life cycle and strive for continuous improvement
- FDA Role: Initial verification, subsequent audit
- No manufacturing supplements (may be needed for formulation change)

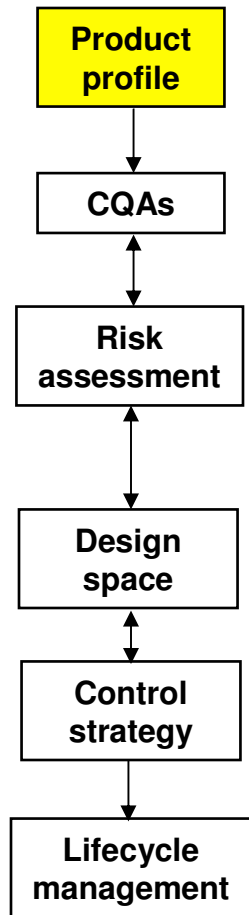
Janet Woodcock, M.D.
Deputy Commissioner/Chief Medical Officer, FDA
Pharmaceutical Quality Initiatives Workshop
March 2, 2007

Example QbD Approach (ICH Q8R1)



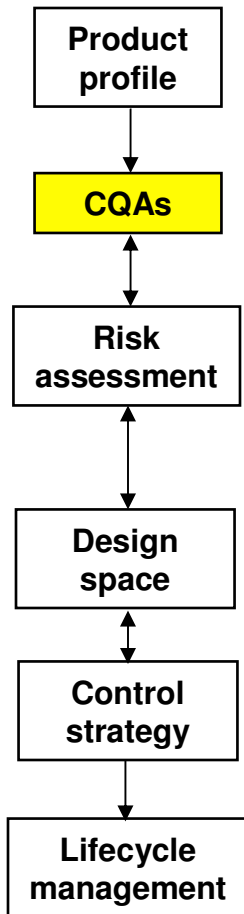
- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

Product Profile



- Product profile considerations
 - dosage form
 - strengths
 - route of administration
 - release/delivery and pharmacokinetic characteristics
 - specific quality criteria (e.g. sterility, purity)
- Dosage form examples
 - tablets
 - inhalation spray
 - parenteral

Critical Quality Attributes (CQAs)



- Definition (Q8R1)
 - A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality
- Can describe aspects of drug substance or intermediates that affect drug product quality
- Drug product CQAs are used to guide product and process development



Example of Critical Quality Attributes

Extended-release product

-CQA from clinical performance standpoint

- dissolution

-CQAs from processability standpoint

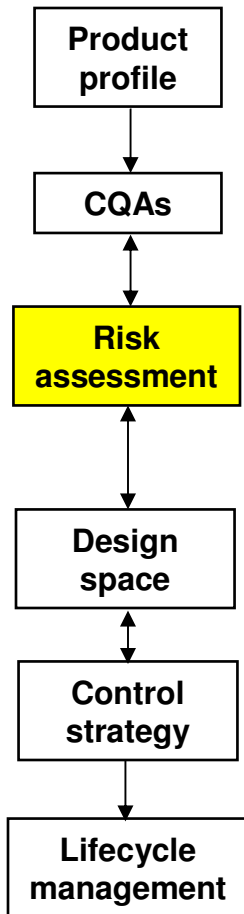
- tablet hardness
- particle size distribution of blend
- appearance



Effect on Clinical Trials

- Formulation selection
- Drug substance characterization
- Drug product performance/development of appropriate CQAs
- Effect on patients
- Potential development of in vitro/in vivo correlation (IVIVC)

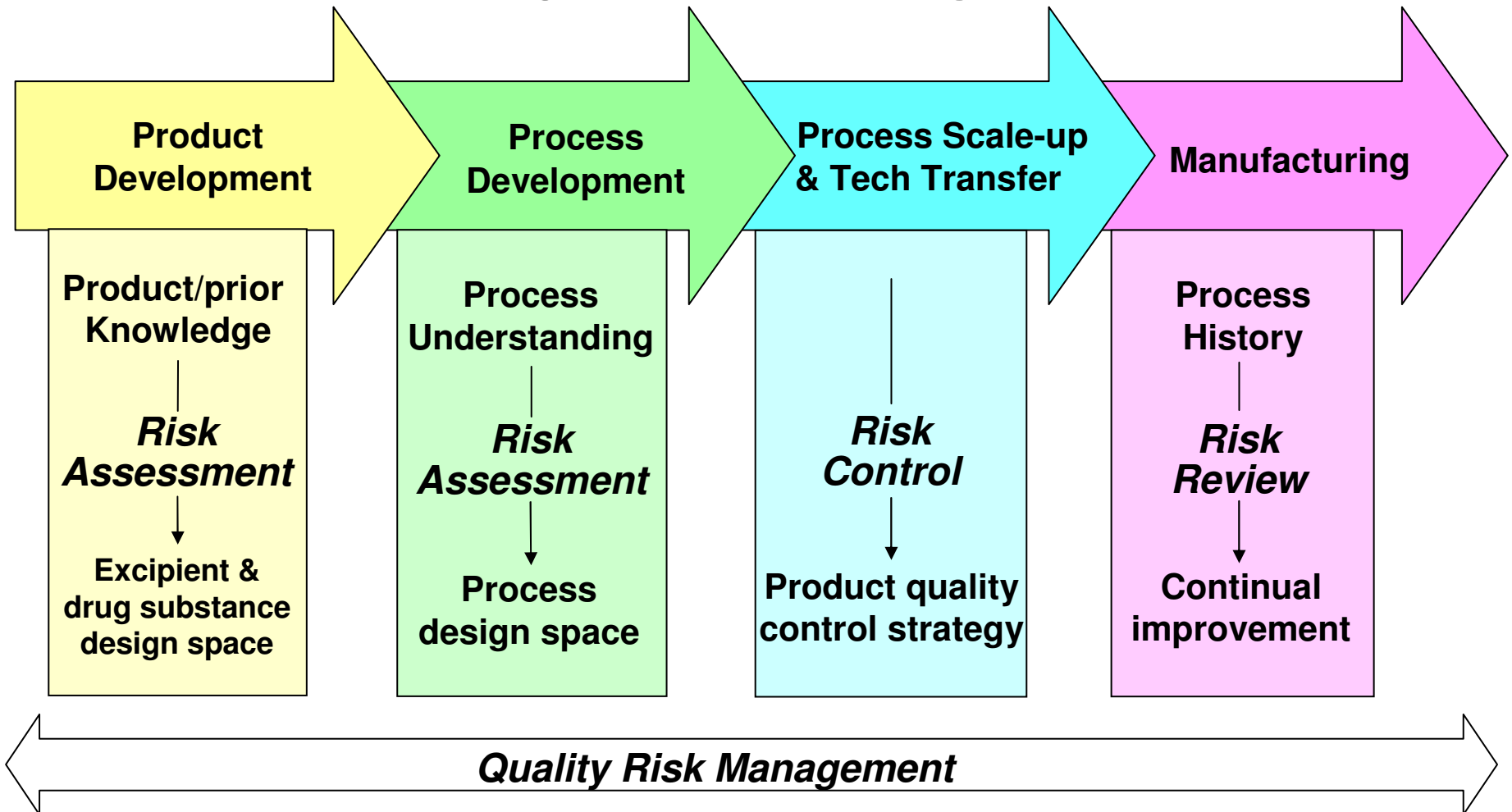
QbD – Risk Assessment (Q8R1)



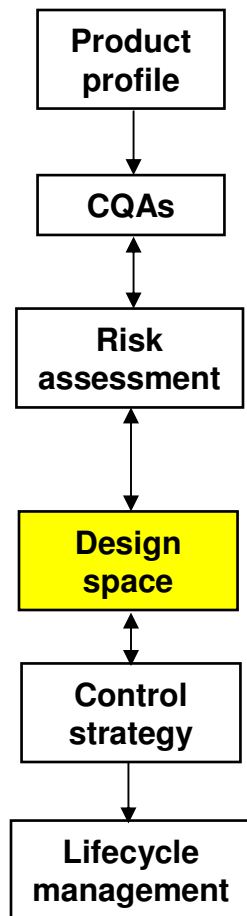
- Prioritize list of potential CQAs
- Aid in identifying and linking material attributes and process parameters which have an effect on CQAs



Quality Risk Management



QbD – Design Space (Q8R1)



- Definition
 - The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters.
- Regulatory flexibility
 - Working within design space is not considered a change
- Design space is proposed by the applicant and is subject to regulatory assessment and approval



When to do QbD?

Timing is at Applicant's discretion

- Phase 1: focus on product understanding
- Phase 2: focus on process understanding
- Phase 3: apply product and process understanding to manufacture of clinical trial supplies and NDA supportive batches

Agency interactions: EOP2, pre-NDA, CMC specific meetings (all are encouraged)



How Does QbD Accelerate Development?

More work upfront

- Systematic
- More thorough results
- Reduces product failures
- Quality control strategies based on product knowledge and process understanding
- A more scientific and risk-based approach to regulatory oversight

You cannot place a price tag on failures that do not occur.



Conclusion

Implementation of QbD is a win-win-win situation

- Manufacturers – Better understanding of product/process, more efficient process, reduced regulatory burden
- Regulators – providing regulatory flexibility without sacrificing quality
- Patients & Caregivers – increased assurance of product quality



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Challenge Questions

- What are the benefits of establishing clinical linkage in a QbD paradigm?
- What are the challenges of establishing clinical linkage in a QbD paradigm?
- What are the challenges of applying QbD to complex drug dosage forms, such as, inhalation products?