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Regulatory Modernization

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Content of Presentation

- Focus of FDA modernization efforts
  - Pharmaceutical manufacturing – pharmaceutical development important part
- Why
  - Why have we changed our regulatory processes?
- What
  - What have we changed them to and what do we hope to accomplish?
  - What are the opportunities and challenges?
- Where
  - Where are we going from here?

FDA Organizational Structure

- Two centers involved in looking at biotech and biological products
  - CBER
  - CDER
- CDER focused on all therapeutic products – small molecules, proteins and monoclonal antibodies
- Review all products for marketing – includes both product development and product manufacturing
- Have responsibility for all innovator products, biotech products and generic products – need for consistency in regulatory requirements
- My presentation is based on what is being done in CDER although CBER has also begun to make similar regulatory changes and is working with us on a number of initiatives

State of Pharmaceutical Manufacturing at Beginning of 21st Century

- Not state-of-art as compared to other industries
- Able to achieve reasonable product quality – but some times at a great effort and cost
- Little emphasis on manufacturing – mainly on development although manufacturing is approximately 25% of expenses
- For some products, waste as high as 50%
- Inability to predict effects of scale up
- Inability to analyze or understand reasons for manufacturing failures
- Globally fragmented

Consequences

- High cost of products due to
  - Low efficiencies in manufacturing
  - Manufacturing time requirements based on testing, etc.
  - Waste
- Drug shortages often due to inability to manufacture
- Lack of improvements in processes although new technologies available
- Slowed development/access for investigational drugs
- All of these things added up to perception that there was a need for more intensive regulatory oversight

State of Regulatory Quality Review Processes at Beginning of 21st Century

- Oversight increased – reviewed every manufacturing change made – increased number of application supplements
- Focused on chemistry but not on engineering and other supporting science
- Implemented numerous changes in processes to facilitate increasing review requirements (SUPAC, BACPAC)
- Issued numerous “how to” guidances (prescriptive)
- All standards internally developed
- PDUFA requirements speed up review process
- More complex products along with new dosage forms
- Increased emphasis on focused issues such as counterterrorism, pandemic, counterfeiting

Consequences

- Increased workload
- Not enough staff to handle
- More and more information from sponsors required and submitted (not always relevant)
- Very little flexibility in process
- Impossible to ensure consistency
- Discouraged innovation because of need for additional regulatory
- Assumed all responsibility for product quality
- Conservative approach

The Desired State: A Mutual Goal of Industry, Society, and the Regulators

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight.

Janet Woodcock, M.D.

Characteristics of the Desired State

- Quality is controlled by industry
- Manufacturers have extensive knowledge about critical product and process parameters and quality attributes
  - Knowledge comes from product development, prior experience, studies, scientific and technical literature
  - Use that knowledge to understand product risk and risk mitigation
  - Use that knowledge to determine appropriateness to make manufacturing changes
- Manufacturers control process through quality systems over life cycle and strive for continuous improvement
- FDA's role is to do initial verification and subsequently audit

Critical Factors to Implementing Desired State

- International harmonization
  - Global market
  - ICH – working toward common set of standards
- Pharmaceutical development information
  - Important aspect of product quality – how product is designed
- Quality risk management
  - Assessment of risk to ensure product quality
- Quality systems
  - Assure product quality through appropriate quality systems
  - Maintain change control process
- Technology
  - Process analytical technologies help in process understanding

Implementation of Desired State

- Drivers –
  - Pharmaceutical Quality for the 21st Century Initiative
  - Critical Path Initiative
  - Quality by Design Initiative
  - Process Analytical Technologies Initiative

Progress Toward Desired State for Product Review

- Just begun - laid the foundation - involves both industry and agency
- Evolution not a revolution
- Incorporation of critical factors
- Both review and inspection involved in modernization
- Implementation of Quality by Design (QbD) in product review – all three review offices

What is “Quality by Design”?

- Quality
  - “Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes.”
- Quality by Design (QbD)
  - “Means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches.”
- “Smart from the Start”
  - Quality should be built in, not tested

New Review Paradigm – Quality by Design

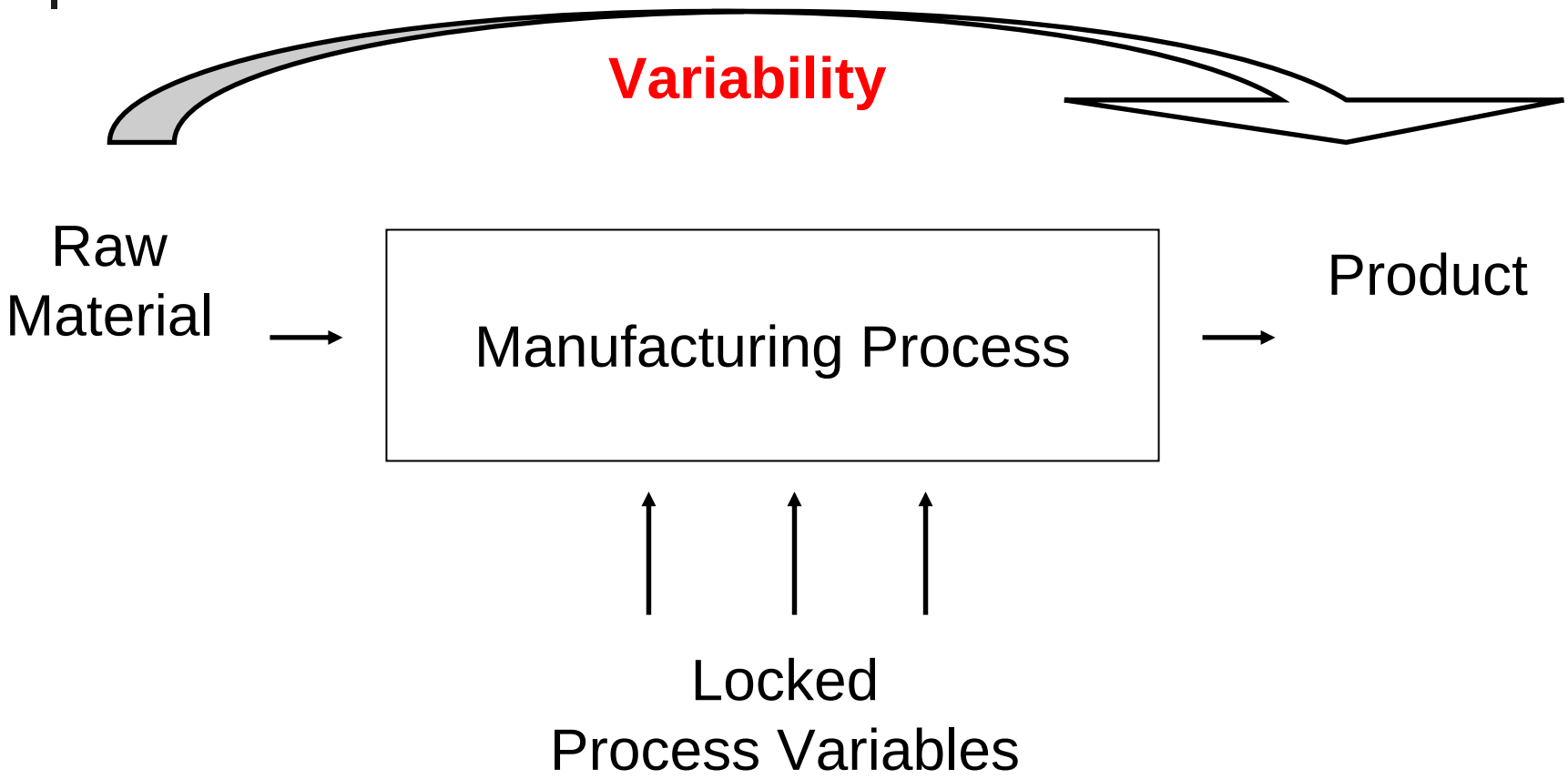
In a QbD system:

- 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 well understood
- The process is continually monitored, evaluated and updated to allow for consistent quality throughout product life cycle
- Critical sources of ***variability are identified and controlled*** through appropriate control strategies

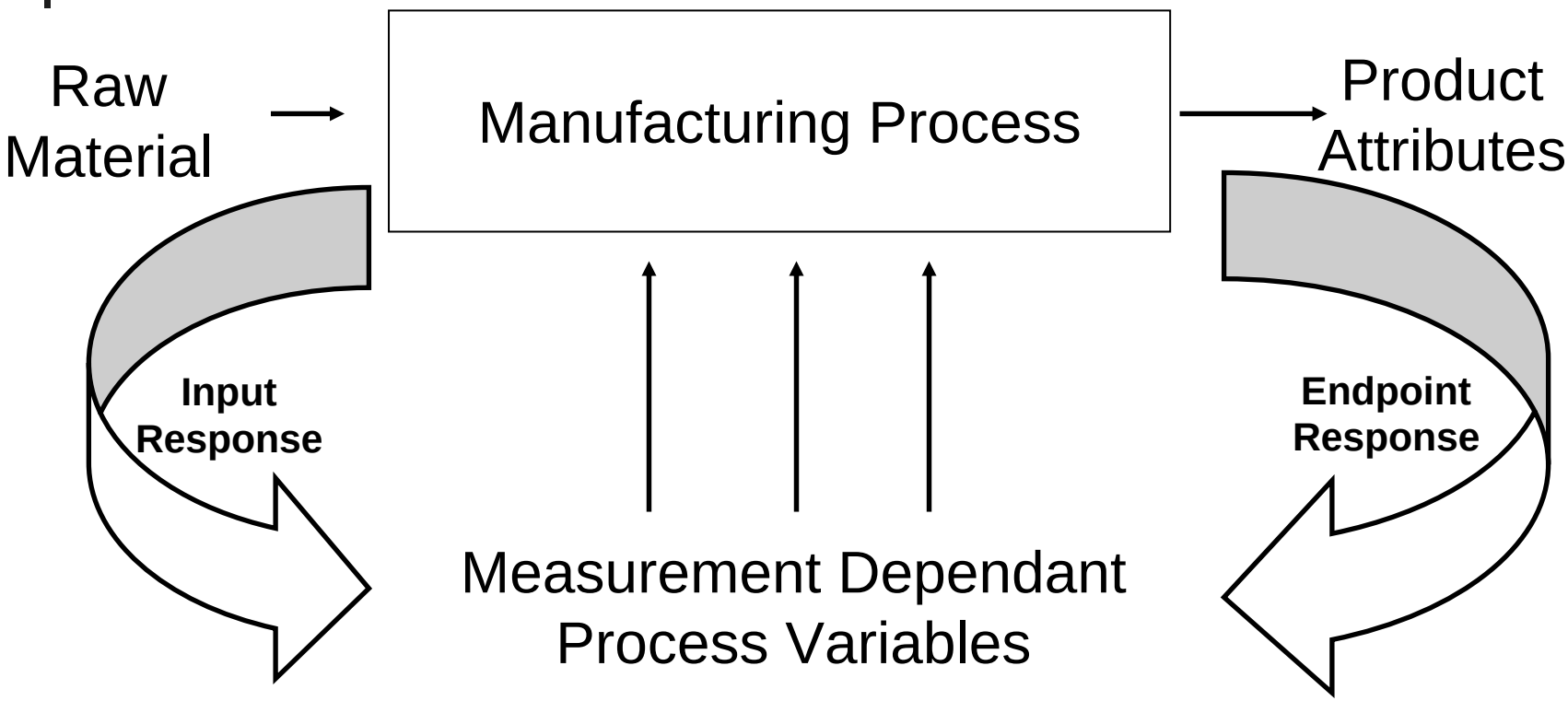
Differences in Approaches

Aspects	Traditional System	QbD System
Pharmaceutical development	Empirical, random, focus on optimization	Systematic; multivariate experiments; focus on control strategy and robustness
Manufacturing Process	Fixed; focus on optimization	Adjustable within design space; continuous verification within design space; managed by company's quality systems
Process Control	In-process testing; off-line analysis	PAT utilized; process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy , real-time release possible
Life Cycle Management	Reactive to problems and to OOS; post-approval changes needed	Continual improvement enabled within design space

Traditional Paradigm



QbD System

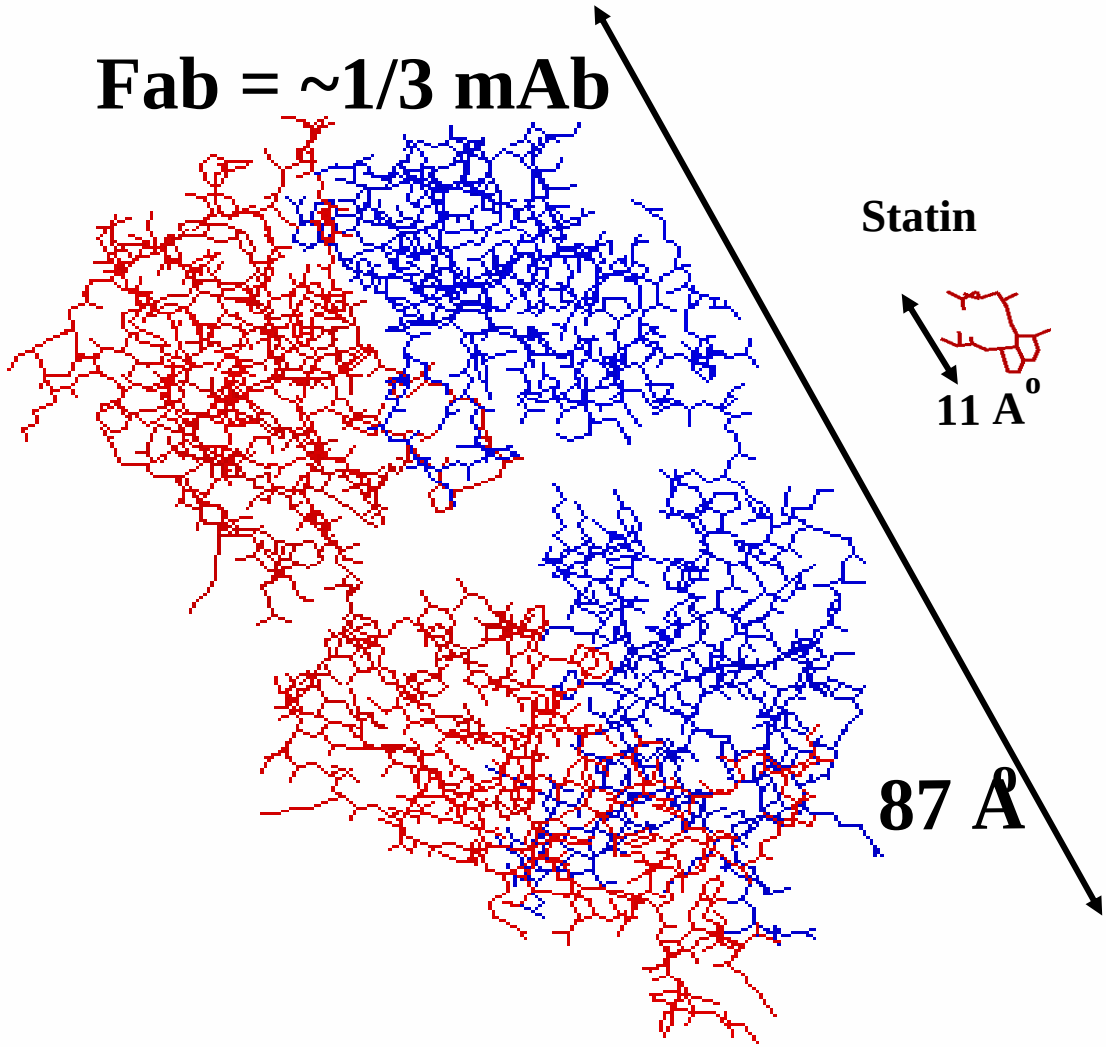

Raw Material
Manufacturing Process
Product Attributes
Input Response
Endpoint Response
Measurement Dependant Process Variables

Specifics for Biotech Products Regarding QbD

- ***Complexity of products requires additional considerations***
- Difficulty in identifying critical quality attributes
- Biological characterization
- Ensuring safety and efficacy

Structure of Complex Products

- 1° structure
- higher order structure
- post-translational modifications
- heterogeneity



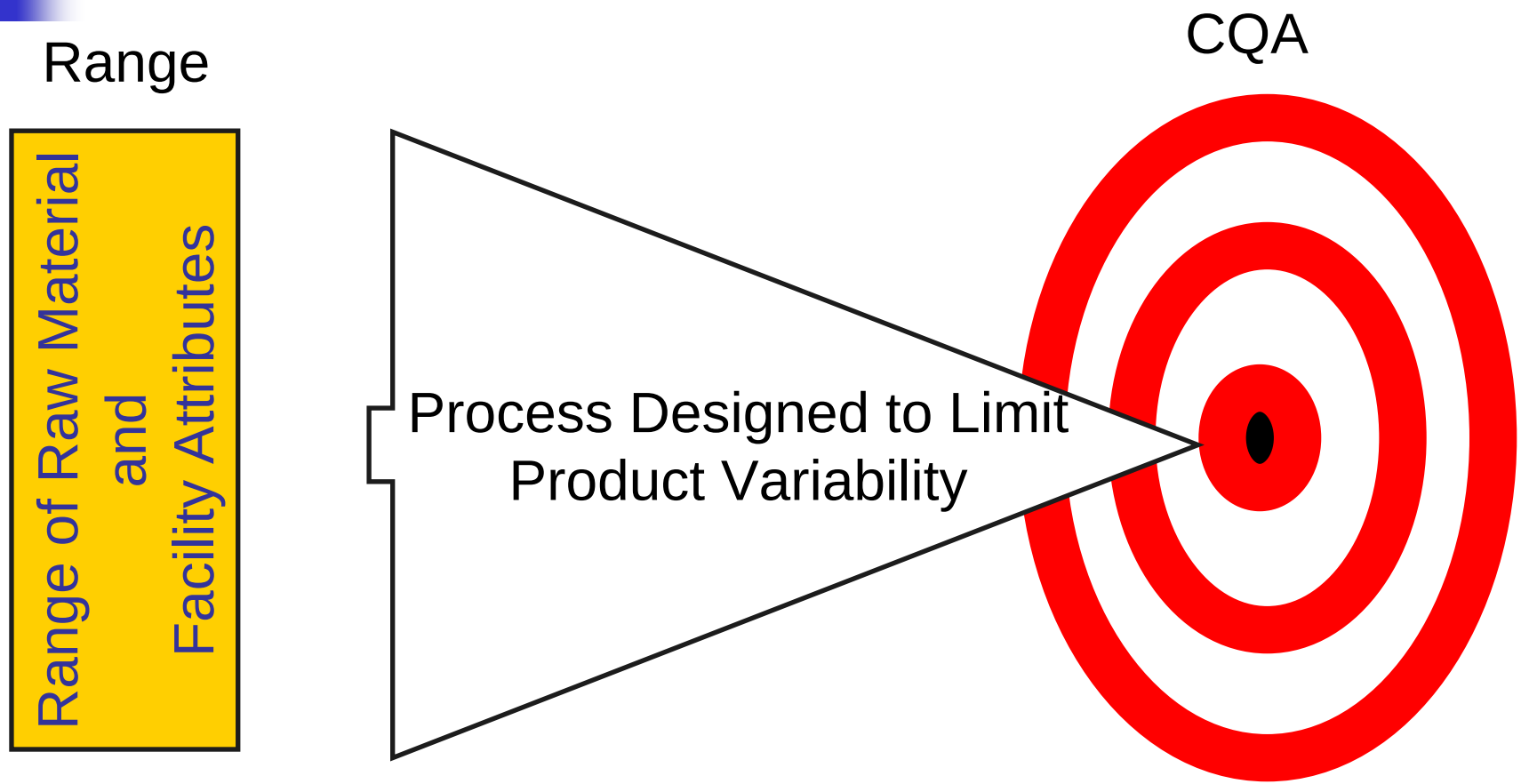
Specifics for Biotech Products Regarding QbD

- Complexity of products requires additional considerations
- ***Difficulty in identifying critical quality attributes***
- Biological characterization
- Ensuring safety and efficacy

Relevant Attributes

- ... those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product (Q6B)
- Can these attributes be defined?
  - Often difficult
  - Default is to look at many attributes
- For QbD need to focus only on critical attributes and the impact of those attributes on safety and efficacy
- Need to develop a design space to be documented in application which is based on CQAs

Target Critical Quality Attributes



Specifics for Biotech Products Regarding QbD

- Complexity of products requires additional considerations
- Difficulty in identifying critical quality attributes
- ***Biological characterization***
- Ensuring safety and efficacy

Characterization

- Need to be sure to understand structure and function
- Difficult to do for many products
- More complex product is, the more difficult to characterize
- Varies some times from lot to lot
- Numerous factors involved
- In QbD, if design space changes for some reason, may have to recharacterize

Specifics for Biotech Products Regarding QbD

- Complexity of products requires additional considerations
- Difficulty in identifying critical quality attributes
- Biological characterization
- ***Ensuring safety and efficacy***

Safety, Efficacy and Quality

- Products need to be designed to ensure safety, efficacy and quality
  - Increasing bioavailability
  - Improving function/new properties
  - Reducing immunogenicity
  - Selective technologies in development such as phage, ribosome and yeast display
- Quality by design
  - These same strategies can also be used to select for product quality and manufacturability

Where Are We Now in Implementation of QbD for CMC?

- All offices implementing ICH Q8 (pharmaceutical development), Q9 (risk management), and Q10 (quality systems
- Process varies from review office to review office
  - ONDQA – implemented QbD – have several applications under the pilot program – promoting other submissions with QbD information – this includes some biotech products (e.g., insulin, growth hormones)
  - OGD – implemented Question Based Review (QbR) – series of questions to help manufacture share knowledge on product and process – questions based on information necessary to ensure QbD
  - OBP - in process of introducing a pilot program for biotech products

Benefits of New Paradigm (For Industry, FDA and the Public)

- Reliably produces high quality medications
- Maximizes efficiency, agility and flexibility in the manufacturing process and regulatory process
  - Reduces the burden on process validation and routine testing
  - Reduces the need for recalls, reworks, reprocessing
  - Eliminates non-targeted inspections
- Promotes continuous improvement and technical innovation while reducing need for manufacturing change supplements – expedites changes for manufacturers
- Provides a science and risk-based approach to development and quality assessment
- Increases scientific exchange between FDA and sponsors
- Promotes consistency in regulatory review and provides for greater transparency
- Distinguishes between information for assessment process and life-cycle commitments
- Results in knowledge rich submissions resulting in efficient and effective oversight
- Facilitates global harmonization

Win, Win, Win

Important Aspects of Implementation

- Quality of products has never been bad – just processes both manufacturing processes and regulatory process need to be modernized and more responsibility for product quality placed on manufacturers
- Looking to provide a system that will ensure quality through a well designed product and process
- QbD is not mandatory
- QbD is positioned to
  - Infuse more science into the regulatory process
  - Allow specifications to be based on product performance requirements
  - Allow more flexibility in regulatory requirements
  - Allow companies to implement new technologies and promote continuous improvements of their products
  - Allow companies to understand and control variability
  - Encourage the use of risk assessment and risk mitigation in manufacturing

Challenges of Implementation of QbD

- Cultural change – both industry and agency
- Developing a consistent understanding of terminology
- Time – it will take time to make necessary changes – in meantime run in parallel to old system
  - Have legacy products which have not been handled the same way
- Determining level of detail in submission needed in order to demonstrate product knowledge and process understanding
  - Will take time to determine appropriate level
  - Pilots beneficial
- Communication - making information available to industry
  - Guidances
  - Presentations
  - Conferences/workshops

Challenges (cont)

- Need more experience in new paradigm for both industry and agency
  - Beginning to see more information
  - Several companies submitted QbD data or met with agency to discuss
- Industry's continuous apprehension in sharing information
- Filling the science knowledge gap both in Agency and in industry
- Resources and growing workloads
- Additional issues for consideration
  - Global regulation
  - Specification setting – clinical experience vs. process capability
  - Risk assessment
  - Process validation
  - Broader comparability protocols
- Other challenges
  - Follow-on biologics

Summary

- Change is happening
- Can visualize a desired state and have taken a number of steps to move in the “right” direction
- Quality by Design important element in achieving desired state
- Beginning to implement across all CMC review programs
- At early stages of process (evolution)
- Special consideration needed for implementing for biotech products
- With opportunities, come challenges
- Tremendous benefits to industry, FDA and the public!