



U.S. Department of Health and Human Services

Food and Drug Administration



Regulatory Modernization and the Quality Endeavor

Joint CVG/Therapeutic Products Directorate (TPD)
Conference and Exhibition

"From Block Buster to Boutique Products – Coping with Changes"
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The Desired State

- Product quality and performance
 - ensured through design
 - Formulation, product and process
 - effective and efficient manufacturing processes
- Specifications: Product and process
 - based on a *mechanistic* understanding
 - how formulation and process factors affect product performance
- Continuous *real time* quality assurance
- Regulatory policies and procedures: Relevant
 - tailored to accommodate ... scientific knowledge

Moving Forward

- Major future opportunity will be better linkage between clinical performance and quality parameters
- This will inform what to measure (and what not to measure)
- Important concept for “Quality by Design”—have to understand parameters of quality

The Goal

- ... is to design and develop well understood processes
 - that will consistently ensure a predefined quality at the end of the manufacturing process.
- Such procedures consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns
 - while improving efficiency
 - Allowing continuous improvement
 - Process Optimization, Product Improvement

Regulatory Modernization Efforts at FDA

- PAT
- Pharmaceutical Quality for the 21st Century Initiative
- Consensus Standards
- ICH Q8, Q9, Q10
- QBD
- QBR
- Process Validation Guidance Revised
- 314.70 Revision
- OPS Quality System
- Pharmaceutical Inspectorate

Modernization Efforts

(1) Quality Systems Guidance for GMPs

- Draft Guidance on how to satisfy GMPs with a comprehensive quality systems approach
- Encourages adoption of risk management approaches and continuous improvement
- Intended to facilitate development of possible Q10 internationally harmonized guideline
- Risk-Based Model for Inspectional Oversight

(2) Risk-Based Model for Inspectional Oversight

- Weighted risk factors: product, process & facility
- Intended to maximize public health impact of inspections
- Intended to create positive incentives for product/process understanding and effective quality systems

(3) Electronic Records (Part 11)

Regulatory Reform

- Final guidance encourages use of electronic recordkeeping by addressing disincentives and regulatory uncertainty
- Narrowing scope of regulatory requirements
- Encouraging more risk-based approach

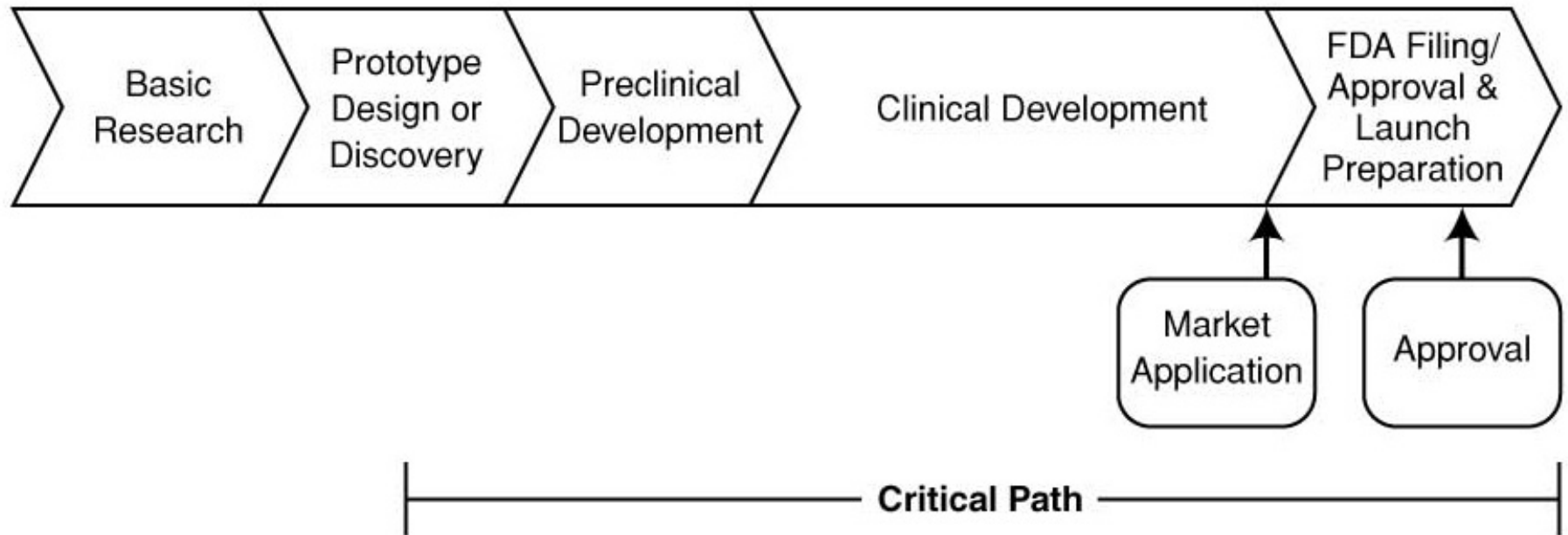
(4) Pharmaceutical Inspectorate (PI)

- Creation of more highly trained cadre of pharmaceutical inspection specialists
- To be trained in latest manufacturing science, technology, and agency policies and procedures
- Will emphasize integration of product specialists on inspection team

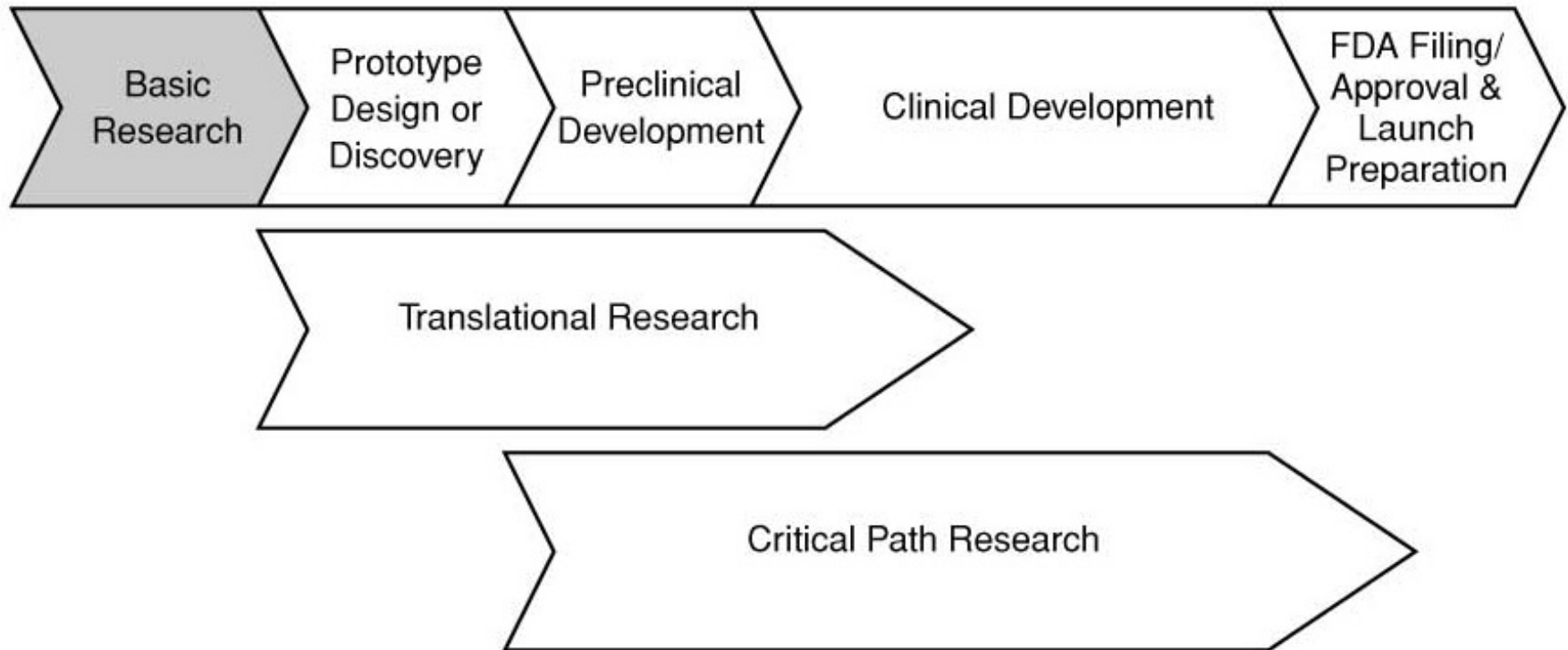
(5) The Critical Path Initiative

- Industrialization dimension
 - Strengthen “Quality – Clinical” connection
 - Sound scientific approaches for calibration and validation of new technologies
 - Encourage development of fundamental science and engineering principles
 - E.g., material (nano-materials) science and processing
 - Support the US pharmaceutical academic programs

The Critical Path for Medical Product Development



Science Underlying The Critical Path of Drug Development



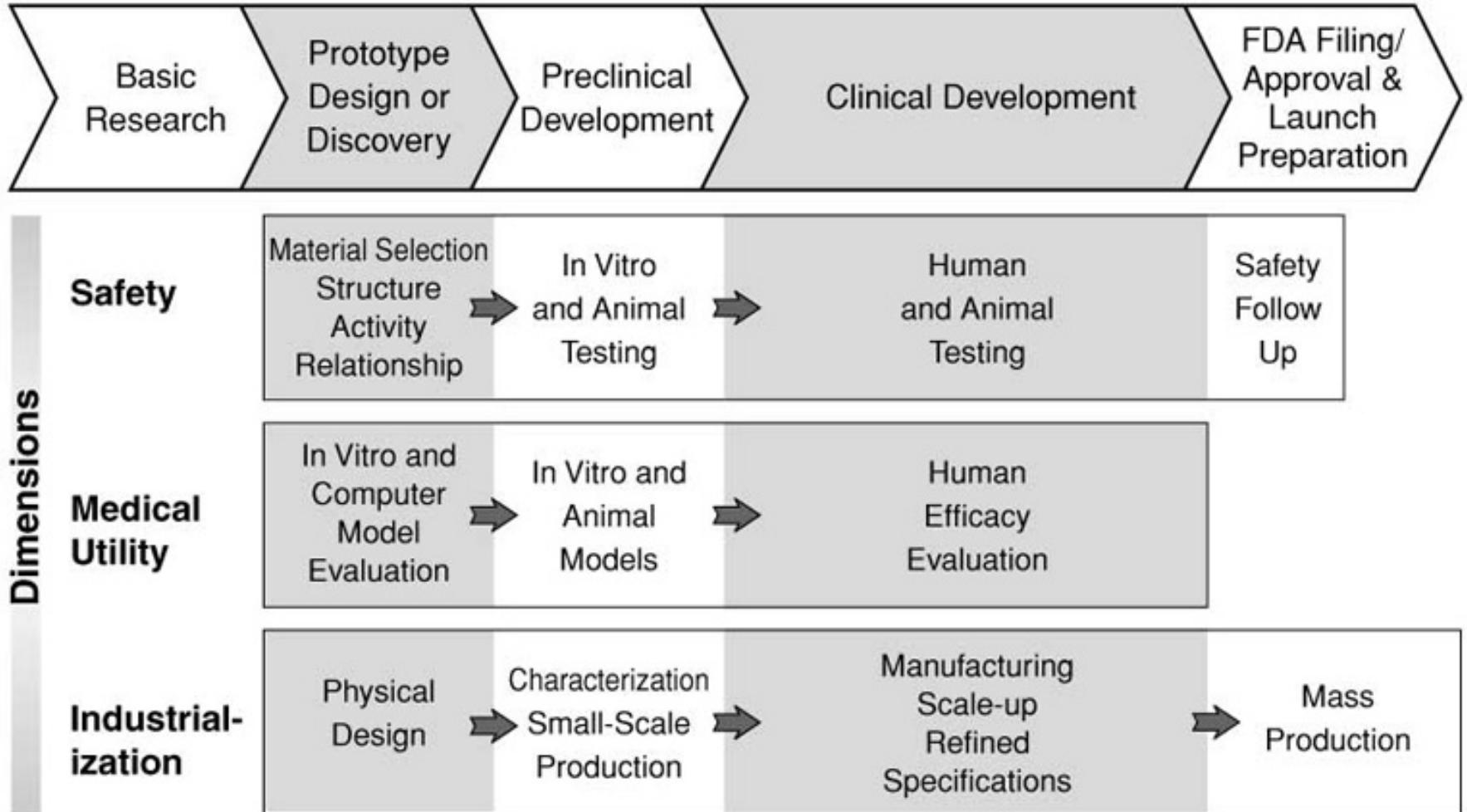
Science to evaluate safety & efficacy of new products, and enable manufacture, is different from basic discovery science

What is on "Critical Path" to Medical Product Development?

Applied science to address 3 key dimensions:

- Assessment of Safety – how to predict if a potential product will be harmful?
- Proof of Efficacy -- how to determine if a potential product will have medical benefit?
- Industrialization – how to manufacture a product at commercial scale with consistently high quality?

Working in Three Dimensions on the Critical Path



(6) Quality by Design

Quality by Design “means that product and process performance characteristics are scientifically designed to meet specific objectives... To achieve QbD objectives, product and process characteristics important to desired performance must be derived from a combination of prior knowledge and experimental assessment during product development.”

Dr. Janet Woodcock, *Am. Pharm. Rev.*, 2004

Quality by Design

- “In a QbD approach 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 and raw materials and process parameters on product quality is understood; and critical sources of process variability are identified and controlled.”

What is Quality by Design?

- Quality by Design means
 - designing and developing formulations and manufacturing processes to ensure a predefined quality
- Quality by Design requires
 - understanding how formulation and manufacturing process variables influence product quality
- Quality by Design is
 - part of an overall quality system (ICH Q10)

Where Are We Now in Implementation of QbD for CMC?

- All offices implementing ICH Q8 (pharmaceutical development), Q9 (risk management), and Quality Systems Guidance
- Varies between review offices
 - ONDQA – implemented QbD – have several applications under the pilot program
 - OGD – implemented Question Based Review (QbR)
 - OBP – introduced pilot program for biotech products

(7) Question-Based Review for CMC Evaluations of ANDAs

- The QbR will transform the CMC review into a modern, science and risk-based pharmaceutical quality assessment that incorporates and implements the concepts and principles of the FDA's *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach* and *Process Analytical Technology* initiatives.
- The main objectives of this enhanced review system are to:
 - assure product quality through design and performance-based specifications,
 - facilitate continuous improvement and reduce CMC supplements through risk assessment,
 - enhance the quality of reviews through standardized review questions,
 - reduce CMC review time when sponsors submit a quality overall summary that addresses the QbR.

(8) Pharmaceutical Quality for the 21st Century Initiative

- Initial goals of the initiative remain our guiding principles:
 - Risk-based orientation
 - Science-based policies and standards
 - Integrated quality systems orientation
 - Strong public health protection
 - International coordination

Modernizing Manufacturing

- FDA's "Product Quality for the 21st Century" Initiative began in 2003
- Goal: Incorporate up-to-date manufacturing and quality science into regulation of pharmaceutical manufacturing
- Prototype for larger critical path initiative
- Modernizing manufacturing theme subsequently incorporated into Critical Path

What does This Have to Do with PAT?

- Critical Path about accelerating pace of introduction of new science/technology into regulation and regulated industry
- PAT emblematic of new way of thinking about pharmaceutical manufacturing
- Move from empirically-derived trial-and-error methods to rigorous, mechanistically-based and statistically controlled processes

(9) Process Analytical Technology (PAT)

PAT is considered to be a **system** for **designing, analysing, and controlling** manufacturing through timely measurements of critical quality attributes and performance attributes..... with the goal of ensuring final product quality.

Changes in Multiple Sectors Required: Product Quality

- Manufacturers will need to change approach, invest in new technology, break down silos between R&D and production, be less conservative
- Internationally, regulators will need to accept and encourage new ways of doing business and harmonize regulatory approaches

(10) Process Validation

- The 'process' of process validation
- Series of activities taking place over the 'life' of the product/process

Lifecycle Approach to Process Validation

- Lifecycle
 - Overall validation is not “complete” but ongoing
 - Requires comprehensive process design to identify and mitigate significant sources of variability
 - achieve process understanding
 - May incorporate risk management
 - Recognizes that more knowledge will be gained during commercial distribution

Lifecycle Approach to Process Validation

- Revised Process Validation Guidance (in progress)
 - Process Design:
 - Lab, pilot, small-scale, and commercial scale studies to establish process
 - Process Qualification:
 - Facility, utilities, and equipment
 - Confirm commercial process design
 - Commercialization:
 - Monitor, collect information, assess
 - Maintenance, continuous verification, process improvement

Process Validation: Stage 1

- Process Design:
- involves defining the commercial-scale process based on knowledge gained through development and scale-up activities.

Process Validation: Stage 2

- Process Qualification: provides confirmation that the process design is functional for commercial scale manufacturing.
- Transfer process design knowledge to production, i.e., technology transfer.

Process Validation: Stage 3

Commercial Production

- Validation in production
- Activities to continually assure that the process remains in a state of control

(11) Supplement Reduction

- Supplement reduction through
 - Modification of 21 CFR 314.70
 - Other in-house activities

(12) Consensus Standards

Laws & Directives

- Congress: National Technology Transfer and Advancement Act (NTTAA); 1995
- Office of Management and Budget (OMB): Circular A-119; 1998 (original in 1993)
- http://standards.gov/standards_gov/index.cfm

Consensus Standards

The Mandate...

- OMB Circular A-119
 - “...this Circular directs agencies to use voluntary consensus standards in lieu of government-unique standards except where inconsistent with law or otherwise impractical.”
 - “This circular applies to all agencies...”
 - “All federal agencies must use voluntary consensus standards in lieu of government-unique standards in their procurement and regulatory activities...”

“Use voluntary Consensus Standards...”

- To determine whether established regulatory limits or targets have been met
- Test methods
- Sampling procedures
- Protocols

FDA Standards Activities

Standards and Technology Team created within OPS

- Coordinates CDER interaction with CSOs and the USP/NF
- Advises applicants and DMF holders about implementation of standards
- Standards Working Group (SWG)
 - Build consensus across FDA for official position on standards-related issues

(13) Quality System- OPS Wide

- Designing and defining the Quality System for OPS
 - Would cover all the review offices within OPS

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Useful Websites

- www.cdrh.fda.gov/science/standards/constand.htm
- www.astm.org
- www.aami.org
- www.standardslearn.org
 - **Why Standards Matter**
 - **US Standards – Today and Tomorrow**
- www.standards.gov