Pharmaceutical Quality for the 21st Century

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May 06, 2008
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CDER Office of Compliance and the Critical Path Initiative

- “Since the initial report, we have broadened our thinking about the Critical Path Initiative to include veterinary medicines, generic drugs, and even foods. For all product areas, the basic idea is to reduce uncertainty about product performance throughout the product life cycle through scientific research. We have set up a large number of collaborations with partners to get this research done, in areas as disparate as drug manufacturing and clinical trial design.”

- Sustainability of product quality throughout the product lifecycle is a major role of the Office of Compliance

FDA Initiatives: A Quality Timeline

Scope of Recent Guidances

ICH Q8/Q8(R) - Pharmaceutical Development
ICH Q9 – Quality Risk Management
FDA Guidance on Quality Systems (9/06)/ICH Q10 – Pharmaceutical Quality Systems

CGMP Revisions

- Modernizing and harmonizing CGMPs
- Phased approach – 1-2-3
- First Phase – ‘non-controversial’:
  - Withdraw proposed 1996 changes
  - Change no asbestos filter to no particle shedding material
  - Potable water can be as defined by, e.g., Japan and EU
  - Equipment needing to be sterilized shall be sterilized

Revisions to CGMP Regulations
CGMP Revisions (cont.)

- First Phase – ‘non-controversial’ (cont.):
  - Eliminate second person check on automated equipment
  - Require sterile container depyrogenation processes to be validated
  - Require bioburden testing, as necessary, on in-process material
  - Require that both aseptic fill as well as other sterilization processes be validated

- Second Phase: ‘substantive’ issues
  - Proposed rule being drafted
  - Includes incorporation of essential quality system elements

Pharmaceutical Quality System

FDA’s Quality System Guidance

- Result of the CGMPs for the 21st Century Initiative – finalized August 2006
- Encourages the use of modern quality management systems
- Emphasizes self-management of change
- Consistent with overall efforts to reduce manufacturing supplements – 21 CFR 314.70 revisions

Pharmaceutical Quality Systems
ICH Q10

Three new letters to learn as we approach the Desired State for pharmaceutical manufacturing in the 21st Century

PQS

ICH Quality Vision - 2003

- A new vision for ensuring product quality (Brussels, July 2003)
- A harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science
  - New ICH guidelines (high level guidelines, more visionary, less prescriptive, flexible regulatory approaches)
  - Pharmaceutical Development (Q8)
  - Quality Risk Management (Q9)
  - Pharmaceutical Quality Systems (PQS) (Q10)
ICH Quality Vision

- Pre-2003: quantitative guidance
- Post-2003: strategic guidance
- Q8/Q9/Q10

ICH Q10 PQS

ICH Q10 Key Points

- Common terminology
- Definition and maintenance of the Quality System
- The role of management, including senior management
- Identification of performance indicators and management of trends to achieve highly capable processes
- Effective change control procedures

ICH Q10 Content

1. Pharmaceutical Quality System
2. Management Responsibility
3. Continual Improvement of Process Performance and Product Quality
4. Continual Improvement of the Pharmaceutical Quality System

ICH Q10 Content (cont.)

1. PHARMACEUTICAL QUALITY SYSTEM
   - Scope / Objectives
   - Relationship of ICH Q10 to
     - Regional GMP Requirements ISO Standards and ICH Q7
     - Regulatory Approaches
   - Enablers
     - Knowledge management
     - Quality Risk management
   - Design & Content Considerations / Quality Manual

ICH Q10 Content (cont.)

2. MANAGEMENT RESPONSIBILITY
   - Management Commitment / Quality Policy / Quality Planning
   - Resource Management / Internal Communication
   - Management Review
   - Oversight of Outsourced Activities
ICH Q10 Content (cont.)

3. CONTINUAL IMPROVEMENT OF PROCESS PERFORMANCE AND PRODUCT QUALITY
   - Lifecycle Stage Goals
     - Pharma. Development
     - Tech. Transfer
     - Manufacturing
     - Product Discontinuation
   - PQS Elements
     - Monitoring
     - Corrective/Preventive Actions
     - Change Management
     - Management Review

ICH Q10 Comments
- Docket in E.U., Japan, & U.S.
- Over 300 unique comments
- Some themes:
  - Integration with Other ICH Q Guidelines
  - Lifecycle: Pharmaceutical Development
  - Definition of “Control Strategy”
  - Regulatory Impact

Potential Opportunities to Enhance Regulatory Approaches

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Potential Opportunity</th>
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<tr>
<td>1. Comply with GMPs</td>
<td>Compliance - status quo</td>
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| 2. Demonstrate effective PQS, including effective use of quality risk mgmt principles (ICH Q9 & Q10) | Opportunity to:
  - increase use of risk-based approaches for regulatory inspections |
| 3. Demonstrate product and process understanding, including effective use of quality risk mgmt principles (ICH Q8 & Q9) | Opportunity to:
  - facilitate science-based pharma. quality assessment
  - enable innovative approaches to process validation
  - establish real-time release mechanisms |

Q10 and Q8 Link
- Processes for pharmaceutical development (Q8 or equivalent) are key linkages to product realization within the Pharmaceutical Quality System.
- Q8 provides for robust development and understanding that serves as the basis for continual improvement.
Q10 and Q9 Link

- The Quality System should encourage and facilitate the use of Quality Risk Management (Q9) approaches throughout the system.
- The design and application of processes within the Quality System should be based on appropriate risk management principles and methods.

Quality by Design (QbD)

- A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (ICH Q8(R), step 2).

Implementation Effects of Science and Quality

- Closer collaboration between R&D and Commercial Manufacturing—Commercialization Initiative
  - Restructuring of plants worldwide bringing in closer proximity development, tech transfer and initial commercial manufacturing
- Opportunity Costs: Tangible business and quality benefits in deviation reduction, health and safety, quality plan conformance, and reduction in manufacturing losses and recalls.
  - System of Integrated Quality Standards in place for Development, Manufacturing, and Product Surveillance
- Integrated Pharmaceutical Quality System Drives Sustainability and Improvement Manufacturing was approximately $200 million under plan for one year, and approximately $70 million under plan the next year due to quality system improvements:
  - Deviations reduced 70%.

CGMP Quality Program Accomplishments CDER, CBER, CVM, ORA

- Coming Soon:
  - Guidance on the Prevention of Cross Contamination of Potent Compounds
  - Technology Transfer Initiative
  - ICH Implementation Working Group
  - Lifecycle Approach to Process Validation Guidance

Where Do the Challenges Lie?

Comments heard:

- How do I release the batch with real time release? Can I default to “traditional end product testing”?
- What is considered Out of Trend Out of Spec and Warrants an Investigation
- What does process validation look like.
Where Do the Challenges Lie? (cont.)

Testing and Release for Distribution: For each batch of drug product there shall be appropriate laboratory determination....
- Doesn't have to be end product
- Real time release is sufficient and does not have to be backed up with "traditional end product testing" nor is it appropriate to substitute at will
- The "need" to do "traditional testing" is covered by stability

Where Do the Challenges Lie? (cont.)

Data, Trends and Investigations: requirement under US CGMP to review annually
- Modern manufacturing methods and controls make this possible in real time
- Not all trends require investigations, however "unexplained discrepancies" do
- Manufacturers should be better able to understand those with real time monitoring and controls

Process Validation

Process Validation for Active Pharmaceutical Ingredients is enforceable under the Statute
- Statutory cGMP provision at 501(a)(2)(b) of the Federal Food, Drug, and Cosmetic Act
- Feasible and valuable
- CGMP guidance available - ICH Q7A

Process Validation Old Approach?

- Two decades old
- Design/development foundation weak
- Emphasizes replication at commercial scale
  - does not promote a fuller process understanding
  - making deviation/problem analysis dubious
  - biased batches
- Does not sufficiently enable appropriate regulatory oversight

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

Commercial Production

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

Monitoring

- Timely monitoring of critical operating and performance parameters
- Monitoring of product characteristics (e.g., stability, product specifications)
- Monitoring adequacy of personnel training and material, facility/equipment
- Investigate problems for root cause and implement corrective action

Periodic Evaluation

- Re-validation – not using this term in the revised Process Validation Guidance
- Production phase monitoring
  - evaluate quality indicator data, changes, and adverse trends
  - periodically decide if new studies, e.g., conformance batches or other verification experiments, need to be done
- Retrospective

FDA’s View of Process Analytical Technologies

- Process Analytical Technology (PAT)
  - a system for designing, analyzing, and controlling manufacturing
  - through timely measurements of critical quality and performance attributes of raw and in-process materials and processes
  - with the goal of ensuring final product quality
- PAT Fundamental Tenets
  - *Quality cannot be tested* into the product; it should be *built-in or should be by design*
- PAT Goals
  - Enhance understanding and control of processes

PAT Tools

- PAT tools can be categorized as:
  - Process analyzers
  - Process control tools
  - Multivariate tools for design, data acquisition and analysis
  - Continuous improvement and knowledge management tools
- *PAT is more than just an analyzer!*
FDA Progress in PAT Implementation

- Training
  - 1st PAT Cadre – 15 investigators and reviewers trained
  - 2nd PAT Cadre – 45 investigators and reviewers being trained
  - Pharmaceutical Inspectorate – training incorporates fundamentals of PAT
  - Reviewer training – multiple sessions on many aspects of PAT

Industry Progress: Examples of PAT Tools in Development

- In-line laser light scattering analyzer to monitor nucleation during crystallization
- FTIR and FBRM (Focus Beam Reflectance Measurement) to understand crystal growth and nucleation
- At-line DSC to monitor crystalline form
- At-line pressure test to force drug substance degradation
- At-line particle size distribution monitoring
- NIR to understand & design blending process

Industry Progress: Examples of Process Analyzers in Manufacturing

- Monitoring only:
  - Assay by on-line measurement
  - Identity by on-line measurement
  - On-line particle size monitoring
- Monitoring and control:
  - Table compression weight check and adjustment
  - Endpoint determination of blending
  - Weight check and adjustment of powder filling operation
  - Adjustment of process parameters based on starting material attributes

Implementation of PAT

- Regulators/FDA Challenges
  - Training reviewers and investigators
  - Developing new approaches for review and inspection
  - Integration of review and inspection
  - Communicating expectations to industry
  - International harmonization
  - Industry's apprehension in adopting new approaches and investing in new technologies
  - Industry's apprehension in sharing information with FDA

Industry Challenges

- Lack of experience in developing and implementing PAT systems
- Training of scientific, operational and regulatory personnel
- Fear of change
- Perceived regulatory risks
- Investment - more resources needed initially
  - Management support crucial
What are the Challenges that Lie Ahead?

- Global Market Place
- Variable Regulation or Understanding of Product Quality
- Economic Pressures and Incentives
- The Need for Industry to Control Sources and Outsourcing of Activities

Thank You