SESSION IV

Mature Pharmaceutical Quality Systems Enabling Ease of Post Approval Change Management

Quality Management Maturity (QMM)

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Current State of Pharmaceutical Quality

- Product Quality is High
  - Pharmaceutical quality is achieved by assuring every dose of a drug on the market is safe, effective, and free of contamination and defects
  - FDA regulatory oversight provides assurance that sites manufacturing for the U.S. market comply with CGMP
- Supply Chain Resilience is Low and Drug Shortages Persist
  - 62% of drugs that went into shortage between 2013 and 2017 were associated with manufacturing or product quality problems.
- The market does not recognize and reward manufacturers for having mature quality management systems
- Simple adherence to CGMP requirements does not indicate that a manufacturer is investing in improvements to prevent supply disruptions

FDA's Vision for Pharmaceutical Quality

- An efficient, agile, flexible manufacturing sector that reliably produces quality drug products without extensive regulatory oversight
- Moving beyond simply meeting CGMP requirements and closer to robust quality management systems
- Managing continual improvement of the process or quality system

Effects to Improve the future state of pharmaceutical quality

- New Inspection Protocol Project (NIPP):
  - To use standardized electronic inspection protocols to collect data in a structured manner.
  - To promote consistent and comprehensive coverage of critical areas of drug manufacturing and provide structured, data-rich reports.
  - To better understand how certain variables (e.g., location of the establishment, type of establishment) affect quality.
  - To inform future inspections, identify policy/outreach opportunities, and influence application-related decision making.
- Quality Management Maturity:
  - To characterize quality management maturity among human drug manufacturers
  - To incentivize drug manufacturers to invest in quality

Quality Management Maturity (QMM)

- To have consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement
- The goals of this program:
  - Foster a strong quality culture mindset
  - Recognize establishments that have advanced quality management practices and strive to continually improve quality management practices
  - Identify areas where quality management practices can be enhanced and provide suggestions for growth opportunities
  - Minimize risks to product availability to assure reliable market supply

Misconceptions about the QMM Program

- QMM assessments are not used to evaluate compliance with CGMP
  - Compliance is a prerequisite for a QMM rating
  - QMM assessments are not part of FDA's inspection authority and participation in the QMM program is voluntary
- QMM assesses manufacturing establishments, not product quality
  - Can not and do not evaluate the quality of specific products
- Maturity is independent of establishment size or age, and the types or number of products approved
  - Focus on evaluating if a culture of quality exists and how this mindset is reflected in the quality practices
- QMM assessments are distinct from the collection of Quality Metrics
  - QMM assessments are qualitative and focus on approach
- QMM is NOT an additional burden or requirement
  - a quality culture should be integral to the quality system

QMM Benefits

- Being more informed about the quality management practices
  - allowing for better resource allocation decisions (e.g., inspection timing and frequency)
  - regulatory flexibility (e.g., related to postapproval changes)
  - move to performance-based regulation
- A robust QMM program will enable CDER to more effectively implement ICH Q12
  - facilitate postapproval changes in a more predictable and efficient manner
  - increase transparency between industry and regulatory authorities, and
  - support innovation and continual improvement
- Reward positive and proactive performance for manufacturers
  - Leads to quality system efficiencies, cost savings and regulatory flexibility
  - Enables continual improvement

A QMM Rating Program

- To incentivize drug manufacturers to invest in achieving Quality Management Maturity (QMM)
- To empower manufacturers to identify ways to improve the effectiveness of their PQSs
- To inform purchasers about the level of QMM at sites from which they purchase drugs
- A collaborative and transparent partnership between FDA, industry, and other stakeholders

Proposed Reporting Areas

- Manufacturing process performance: This can include the proportion of lots that were accepted in a given time period as well as the proportion of lots manufactured without a non-conformance;
- Pharmaceutical quality system (PQS) effectiveness: This metric can include the effectiveness of CAPA which can cover the number of CAPAs initiated or closed on time;
- Laboratory performance: This can include the proportion of laboratory test that are completed on schedule;
- Supply chain robustness: This can include the extent to which shipments are delivered on-time and containing the correct quantity.

Considerations for a QMM Rating System

- Clearly define the scope and meaning of QMM ratings
  - ratings reflect the maturity at a manufacturing site and not the quality of the product or the process used to make it
  - a high rating actually means that the site has a history of quality management that goes above meeting regulatory requirements
  - clearly separate QMM assessments from regulatory compliance
  - Compliance is a prerequisite for a QMM rating
- The value of using QMM ratings in purchasing decisions
  - the current perception is that quality of all kinds exists fundamentally if the drug has been approved by FDA
  - have supply chain information to use QMM site ratings in drug purchasing decisions

Key Elements of a QMM Rating Program

- Quality culture must be foundational for mature quality management
  - Senior management must take ownership for quality
  - Staff at every level an organization must contribute to the commitment to quality
- A QMM assessment tool must be objective and consistent across manufacturing sites
- A standardized and validated QMM assessment tool
- Clear incentives for industry to achieve higher QMM
- Transparency is critical in establishing a QMM rating system

QMM Assessment Tool

- CDER is developing its QMM Assessment Tool to evaluate how effectively establishments monitor and manage quality and quality systems covering five practice areas.
  - Management Commitment to Quality
    - how management prioritizes and establishes quality goals and policies
    - how effectively these goals are communicated to staff at all levels in an organization
  - Business Continuity
    - how effectively an establishment builds redundancies into its supply chains to continue operations
    - how well an establishment understands and mitigates risks inherent to its supply chain
  - Advanced Pharmaceutical Quality System (PQS)
    - approach to quality risk management (QRM), process and product quality monitoring
    - manufacturing operations improvement, and CAPA effectiveness checks
  - Technical Excellence
    - implementation of advanced manufacturing and analytical methods that are fit for purpose, driving operational excellence
  - Employee Engagement and Empowerment
    - how willing employees are to making suggestions that can improve manufacturing operations
    - whether leadership creates an environment that encourages employees to share their thoughts and ideas

Assessment of QMM Using a Protocol

- A question based standardized assessment protocol
  - a pre-interview questionnaire in preparing for the assessment questions
  - an onsite or hybrid assessment
  - provide documentation and/or examples to support the answers
- Information from QMM assessments is not intended to evaluate compliance
- The assessment team will evaluate the practice and quality culture
  - Develop and implement risk management plan to mitigate potential supply disruptions
  - Evaluate effectiveness from the product lifecycle and other data (customer feedback)
- The protocol should be executed by assessors trained in both QMM and GMP

Revision to the CP7356.002 - Drug Manufacturing Inspections

- The objective on the effectiveness of quality system:
  - Gain insight into the effectiveness of a drug manufacturer's quality system.
  - Inform understanding of practices at a facility that not only support meeting CGMP compliance requirements but also promote a quality culture that allows for exceeding this standard.
- Manufacturers can demonstrate practices that are indicative of mature quality practices for exceeding CGMP requirements.
  - focus on implementing continual improvements
  - use the latest innovations to enhance control
  - create a culture of quality where leadership demonstrates a commitment to quality and promotes employee engagement and empowerment.
- For manufacturers with a more advanced quality system, FDA may exercise a more flexible regulatory approach, leading toward the goal of producing high quality drug products without extensive regulatory oversight

Indicators of an Advanced Quality System

- Management Responsibility
  - Communication and reward system for employees to bring quality issues to the attention of management
  - Monitoring of external regulatory and business environments to identify unexpected risks to quality
  - Increased levels of personnel understanding, ownership, and engagement that create company-wide quality commitment
- Investigations
  - Effective use of standardized tools to determine a potential root cause
- Corrective Actions and Preventive Actions
  - Routine meetings to collect feedback, reduce operational risks, and ensure initiation of corrective actions and preventive actions
- Supply Chain and Contracted Service Management
  - Consistently meeting planned time frames for product delivery to the customer or internal stock because of high manufacturing robustness (i.e., avoiding delays caused by manufacturing quality problems)
  - Active solicitation and analysis of customer feedback (beyond solely complaints) related to quality and delivery

Indicators of an Advanced Quality System

- Training Program
  - Extensive staff training on advanced quality assurance tools to improve process capability
  - Training on the impact of poor quality on the patient
- Quality Oversight
  - Electronic systems that use analytics to optimize implementation of knowledge management related to products, processes, and components
  - Continual improvement program to optimize quality indicator metrics
- Process Parameters, Product Quality Monitoring, and Annual Product Review
  - Programs to improve manufacturing processes by adopting the latest beneficial innovations and technologies

Revision to the CP7346.832: Preapproval Inspections

Objective 4: Commitment to Quality in Pharmaceutical Development

- Assess the pharmaceutical development program by evaluating the extent to which it is supported, defined, managed, and continuously assessed for its effectiveness as well as its use in supporting continual improvement of the PQS.
- On the initial PAI, periodically on subsequent PAIs, with frequency based on risk.
- When there have been major changes to the quality system, management team, or corporate structure.
- Used for data analysis or internal trending by FDA and may assist in identification of risk factors (e.g., risks related to process, firm history, and product) for future PAI decisions
- helps FDA's decision-making related to the firm's effectiveness in developing new products and integrating changes within an establishment
- provides an opportunity for investigators to observe and document examples of mature quality practices that exceed CGMP requirements and are indicative of an advanced quality system

Revision to the CP7346.832: Preapproval Inspections

- Objective 4 elements supportive of the firm's commitment to quality during development Pharmaceutical Development Program
  - Senior Management Commitment to Quality
  - Multidisciplinary Integrated Development Team
  - Quality Risk Management in Development
  - Failure to conform with an element should not be cited on Form FDA 483 unless the discrepancy or the deficiency can be linked to a CGMP violation
- Cite significant CGMP discrepancies or deficiencies that are identified with Objective 4 coverage on under Objectives 1, 2, or 3, as applicable.

Learning from the QMM Pilot Program

The QMM Pilot Program

- Goal: to support the development of a system to measure QMM based on objective indicators.
- Two pilot programs: between October 2020 and March 2022
  - Criteria: surveillance inspections within 5 years were classified as no action indicated (NAI) or voluntary action indicated (VAI).
  - for eight domestic FDF and seven international API manufacturers, all voluntary participants
- A summary of the lessons learned from the pilots was recently published (Lessons from CDER's Quality Management Maturity Pilot Programs).

The QMM Pilot Program

- The pilot program's QMM assessments were intended to determine:
  - the level of integration of the quality system and quality objectives with business and manufacturing
  - operations at an establishment
  - the agility of an establishment in responding to unexpected changes (e.g., supply chain disruptions, demand surges, deviations, natural disasters)
  - the resilience of an establishment's business and production processes

Learning from Pilot Program

- The QMM assessments are significantly different from regulatory inspections
  - Advance engagement with expectations for the assessment process and outcomes
  - The types of documents could substantiate the QMM ratings
- The assessments were more efficient when the appropriate staff were available to address relevant practice areas
  - Corporate leaders who have responsibilities across multiple establishments and establishment personnel
  - independent on-site interviews with management and staff to gauge the culture at an establishment
- Compound questions that covered multiple aspects of a particular topic within a practice area posed a challenge to some participants
- To develop objective criteria to recognize the maturity levels in a consistent, unbiased, data-driven, and scientific manner.
- To train assessors on the assessment tool, CGMP regulations, and quality guidance documents so that they can distinguish between behaviors that meet or exceed CGMP expectations.
- To train assessors in interview techniques to effectively engage staff at the establishment and efficiently manage time.

Potential Benefits for Participating Sites

- Identification of continuous improvement opportunities
- Improved supply chain insights (e.g. Ratings of API suppliers or contract manufacturers)
- Incentives that might be offered by FDA
- Ability to use results in marketing
- Incentives from purchasers

Learning from Recent Inspections

- Deficiency in Management Commitment to Quality
  - Your firm lacks a QU and approved written procedures defining QU responsibilities and controls.
    - quality control unit failed to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP
    - failed to establish adequate written procedures for production and process control
  - Failed to provide adequate data to demonstrate you validated your drug manufacturing processes to ensure consistent product quality.
    - distributed various drug products which lacked product-specific validation protocols with pre-approved acceptance criteria.
    - failed to adequately qualify your drug manufacturing equipment.
- Deficiency in Manufacturing process performance
  - Lack of a comprehensive assessment and remediation plan to ensure your QU is given the authority and resources to effectively function.

Final Thoughts

- A QMM rating system will foster a more robust drug supply chain and greater commitment to quality in pharmaceutical manufacturing
- The FDA will benefit from QMM ratings by being more informed about the quality management practices at sites, allowing for better resource allocation decisions and regulatory flexibility
- Pharmaceutical companies will get more insight into the robustness of their supply chains
- Purchasers and payors will get more insight into the supply chain of the drugs they buy or reimburse
- Patients, pharmacies, and healthcare professionals get improved clinical care via medicine less at risk of quality-driven shortage

Thank you