CENTER FOR DRUG EVALUATION AND RESEARCH

CDER's Quality Management Maturity (QMM) Program: Practice Areas and Prototype Assessment Protocol Development

White Paper | 2023

Introduction

FDA's Center for Drug Evaluation and Research (CDER) is establishing a program to promote quality management maturity (QMM) at drug manufacturing establishments. CDER is developing its QMM Assessment Tool (protocol and rubric) to evaluate how effectively establishments monitor and manage quality and quality systems. The QMM program aims to encourage drug manufacturers to implement quality management practices that go beyond current good manufacturing practice (CGMP) requirements.[1] The goals of this program are fourfold:

1. *Foster a strong quality culture mindset*

2. *Recognize establishments that have advanced quality management practices and acknowledge establishments that strive to continually improve quality management practices*

3. *Identify areas where quality management practices can be enhanced and provide suggestions for growth opportunities*

4. *Minimize risks to product availability to assure reliable market supply*

Adopting mature quality management practices supports a more reliable drug supply chain by reducing the occurrence of quality-related failures and improving the ability of establishments to maintain performance during expected and unexpected supply chain disruptions. Integrating business and manufacturing operations with quality practices and technological advancements can help achieve higher levels of maturity. This can optimize manufacturing process performance and product quality, enhance supply chain reliability, and foster proactive continual improvement. The next critical step in implementing this program is developing the protocol that assesses the QMM of manufacturing establishments. This prototype assessment protocol will be tested and refined during the 2024 calendar year.

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[1] Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). See also the implementing regulations at 21 CFR part 210 and part 211 for finished pharmaceuticals.

Background

In 2019, the multiagency Federal Drug Shortage Task Force published its report *Drug Shortages: Root Causes and Potential Solutions*. It found that 62% of drugs that went into shortage between 2013 and 2017 were linked to manufacturing or product quality issues. These issues included substandard manufacturing establishments and quality defects in finished products.[2] Quality issues continue to be the leading cause of supply disruptions.[3] Resolving these problems requires establishments to devote time and resources to implement remedial actions. The Drug Shortage Task Force identified that one of the contributing factors to drug shortages is the failure of the market to recognize and reward manufacturers with mature quality management systems that promote the early detection of quality problems and the proactive optimization of business operations.

Between October 2020 and March 2022, CDER worked with third-party contractors to execute two pilot programs aimed at assessing the QMM of drug manufacturing establishments. One pilot program involved seven domestic establishments responsible for manufacturing finished dosage form products and the other pilot included eight foreign establishments that produce active pharmaceutical ingredients (API). These pilots provided valuable insights to CDER for developing a protocol to assess QMM, understanding assessor behaviors, and gathering participant feedback on assessment questions, reports, and outcomes.

On November 2, 2022, the Pharmaceutical Science and Clinical Pharmacology Advisory Committee met to consider the potential impacts of CDER's QMM program on the pharmaceutical industry, drug shortages, and supply chain reliability. In a unanimous vote, the advisory committee expressed its support for the development of CDER's QMM program. CDER has used the findings from the two pilot programs, incorporated the lessons learned,[4] and considered discussions and comments from the advisory committee to shape the development of the QMM program.

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[2] U.S. Food and Drug Administration, Drug Shortages: Root Causes and Potential Solutions (Revised) (2020). Available at https://www.fda.gov/media/131130/download.

[3] See D Gilbert, 2023, How troubles at a factory in India led to a U.S. cancer-drug shortage, Washington Post, accessed August 21, 2023, https://www.washingtonpost.com/business/2023/06/27/cancer-drug-shortage-generics and C Rowland, 2023, The albuterol shortage is about to get worse, Washington Post, accessed August 21, 2023, https://www.washingtonpost.com/business/2023/03/01/drug-shortages-manufacturing-albuterol.

[4] J Maguire, A Fisher, D Harouaka, N Rakala, C Lundi, M Yambot, A Viehmann, N Stiber, K Gonzalez, L Canida, L Buhse, M Kopcha, 2023, Lessons from CDER's Quality Management Maturity Pilot Programs, AAPS J, 25(14).

Assessment of QMM Using a Protocol

The QMM of a drug manufacturing establishment may be best evaluated by a team of assessors using a standardized protocol.[5] The use of teams and a standardized protocol is intended to minimize bias and individual subjectivity in the assessment. The teams could be made up of FDA staff, third-party contractors, or a combination. The prototype assessment protocol may include a series of questions to elicit responses that lend themselves to an assessment of an establishment's maturity.[6] Establishments participating in the QMM program may receive a pre-interview questionnaire that will assist them in preparing for the assessment questions. During an onsite or hybrid (i.e., a mix of virtual and onsite discussions) assessment, establishments may be requested to provide documentation or to describe examples to support the answers provided. This information would solely be intended to substantiate responses to assist in identifying areas of strength and potential areas for growth in terms of quality culture. Information from QMM assessments is not intended to evaluate compliance with CGMP or support regulatory actions.

The purpose of this approach is to create an environment where assessors and establishments can be open and transparent during the assessment. The pre-interview questionnaire will help frame the discussions during the onsite or hybrid assessment. The use of a pre-interview questionnaire coupled with interactive discussion between the assessment team and establishment allows for a more accurate evaluation of the establishment's QMM, provides valuable insights into quality management policies and practices, and permits the development of meaningful recommendations for improvement. The assessment process is designed to support establishments in improving their quality practices and promoting a strong quality culture.

The assessment teams will evaluate the practices and quality culture within an establishment. For example, assessors will examine how the establishment develops and implements a risk management plan to mitigate potential supply disruptions. Assessors will also evaluate how effectively an establishment leverages information gained from different stages of the product lifecycle (e.g., from product development through postapproval marketing) and other data (e.g., customer feedback) to drive improvements to their quality practices.

Given the specialized nature of CDER's QMM assessment, the prototype assessment protocol is best executed by assessors well-versed in both QMM and CGMP. Their training and experience will enable them to differentiate between QMM and CGMP and appreciate where the concepts inform each other. The full prototype assessment

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[5] CDER envisions a base standardized protocol that may be modified with sector-specific questions, as appropriate.

[6] Examples for each practice area are provided in the Protocol Practice Areas section of this document.

protocol is intended to accommodate assessments conducted onsite or using a hybrid approach. To facilitate participation and implementation, it may also be possible to conduct the assessment using a selected subset of practice areas when agreed to by the establishment and FDA. We envision that the assessment involving direct engagement[7] with the establishment will take two-to-five business days.

At the conclusion of each assessment, participants will receive a report highlighting areas the establishment may wish to consider for continuous improvement. Depending on the demographics of participating establishments, number of program participants, and data available to the agency, the report also may benchmark the participant's maturity against similar establishments (e.g., API manufacturers, OTC manufacturers) participating in the QMM program, and may characterize how participating establishments' supply chain reliability compares more broadly to pharmaceutical industry performance as a whole. The benchmarking data would not disclose the identity of establishments that participate in the QMM program; it would simply show how an establishment compares to other establishments based on the selected filters (e.g., establishment size, product type, assessment year).

Prototype Assessment Protocol Practice Areas

CDER is developing a prototype assessment protocol covering five practice areas:

1. *Management Commitment to Quality*

2. *Business Continuity*

3. *Advanced Pharmaceutical Quality System (PQS)*

4. *Technical Excellence*

5. *Employee Engagement and Empowerment*

These practice areas were identified through a comprehensive review process. This process involved examining the literature on quality management including existing programs that evaluate elements of quality culture or pharmaceutical quality, surveying external stakeholders, gathering feedback from partner offices and centers within FDA, and evaluating data from the two QMM pilot programs developed and performed by third-party contractors, in addition to feedback from pilot participants. By conducting a

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[7] This phase of the assessment would include conducting interviews and visiting the establishment.

survey of similar initiatives undertaken by external stakeholders,[8] we gained valuable insights into the content of the practice areas and the scientific aspects of performance measurement. CDER also collaborated closely with our FDA partners to understand quality performance trends and learn from their experiences with similar efforts.[9] The QMM pilot programs provided insight into the process of the assessment and best practices for engaging with participants. Additionally, we reviewed case studies based on the development and implementation of ICH Q9(R1), ICH Q10, and ICH Q12, as well as industry standards (e.g., ISO 9000 Series of Standards).[10]

The following section describes each practice area, provides examples of elements considered in an assessment, and explains why each practice area is important to QMM.

1. *Management Commitment to Quality*

The commitment of all levels of management is necessary to establish a company-wide commitment to quality. Leadership plays a crucial role in ensuring the quality, safety, purity, and identity of drugs delivered to patients and consumers. Management bears the responsibility for setting the tone and modeling a culture of quality within the organization. Management is responsible for establishing the quality policy and objectives, ensuring that these objectives are prioritized, and aligning them with the business objectives and strategic plan. Management is also responsible for allocating the necessary resources to support quality objectives and continual improvement activities. Effective communication is vital to fostering a commitment to quality. Managers play a central role in facilitating clear and open communication channels throughout the organization.

Elements that may be reviewed under this practice area include how management prioritizes and establishes quality goals and policies, and how effectively these goals are communicated to staff at all levels in an organization. The assessment may also cover the effectiveness of management review, including how often they perform their review, to what depth they review data, and how they use the outputs of the review process to initiate continual improvements.

The management of less mature establishments may not align quality objectives

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[8] Examples include the International Society for Pharmaceutical Engineering's Advancing Pharmaceutical Quality Guides, Parenteral Drug Association's Quality Culture Tool, and the University of St. Gallen's Operational Excellence Benchmarking approach.

[9] Examples include the Center for Devices and Radiological Health's Voluntary Medical Device Manufacturing and Product Quality Pilot Program.

[10] See the ICH guidances for industry *Q9(R1) Quality Risk Management* (May 2023), *Q10 Pharmaceutical Quality System* (April 2009), and *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* (May 2021). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

with business objectives, and therefore may not allocate resources to quality improvement projects. Management may not ensure that their quality policy or goals are documented, or they may not communicate the quality policy or objectives to establishment personnel at all levels within an organization. By contrast, the management of more mature establishments will integrate quality into their business goals and strategic plans and ensure resources are made available to meet clearly defined quality goals that are known and understood by staff throughout their organization.

2. Business Continuity

Business continuity ensures that business operations are sustained during expected or unexpected disruptions so that patients have access to a reliable supply of drug products. Successful development of business continuity plans can help establishments minimize economic losses by ensuring continuity of operations. Given the complexity and interdependencies in the pharmaceutical supply chain, it is essential to design operations and supply chains to safeguard against potential disruptive events, thus ensuring supply reliability. Building mature systems relies on effectively identifying hazards, analyzing and mitigating risks associated with those hazards, implementing good governance, and establishing robust monitoring programs. Such monitoring programs serve as early warning systems, enabling the rapid detection or prediction of disruptions to business operations.

Elements that may be reviewed under this practice area include how effectively an establishment builds redundancies into its supply chains to continue operations even when there are sudden changes in the availability of raw materials or packaging materials. This is tied to how well an establishment understands and mitigates risks inherent to its supply chain (e.g., through the development of effective risk management plans). The assessment may also cover the effectiveness of an establishment's preventive maintenance program, how frequently they experience production disruptions because of unplanned maintenance to their facilities or equipment, and how quickly they can overcome these disruptions to ensure a steady supply of products.

Less mature establishments may not thoroughly understand the complexities and risks inherent in their supply chains, and therefore, may develop limited risk mitigation strategies that may not be effective in managing unexpected disruptions. More mature establishments will have insight into the complexity and risks inherent in their supply chains, implement effective cybersecurity measures, develop effective risk management plans, forecast demand, qualify backup suppliers, and optimize inventory levels so that they can effectively respond to unexpected disruptions.

3. Advanced PQS

Establishments implement practices and procedures to support and sustain robust quality systems consistent with CGMP to produce drug products that meet expected identity, strength, purity, and quality characteristics. An advanced PQS effectively uses quality principles (e.g., quality by design) and risk management approaches to ensure its continued suitability, capability, and reliability to minimize disruptions to drug production operations. Establishments that cultivate an advanced PQS benefit from gains in production efficiencies and improved process performance and product quality, which can lead to reduced costs and greater customer satisfaction. Enhancements to the PQS can also help to ensure a more reliable supply of quality drug products by minimizing the occurrence of quality-related failures that can provoke drug shortages.

Elements that may be addressed under this practice area include the establishment's approach to quality risk management (QRM), the rationale for monitoring their process performance and product quality monitoring systems, understanding how the establishment leverages corrective actions and preventive actions (CAPAs) and information from process performance and product quality monitoring activities to improve their manufacturing operations, the rationale governing how a corrective or preventive action is determined to be effective, and the establishment's change management system's ability to effectively evaluate, approve, and implement changes properly.

An advanced PQS implements a systematic process for the assessment, control, communication, and review of risks to the quality and availability of the drug product across the product lifecycle. A proactive approach to QRM can minimize the occurrence of quality-related failures and is of foundational importance in achieving an effective PQS. Less mature organizations may invest in corrective actions in reaction to failures, but do not devote resources to preventive actions to mitigate potential failure modes. More mature establishments utilize QRM principles and leverage knowledge throughout the lifecycle to make informed and timely decisions, and proactively review risks at an appropriate frequency to drive continual improvement and ensure availability of drug products.

4. Technical Excellence

Technical excellence involves effectively managing information and data. This includes understanding the needs, capabilities, and limitations of operations, investing in learning, and adopting new technical skills. Technical excellence also includes implementing innovative manufacturing processes or novel solutions to problems impacting any aspect of the business (e.g., manufacturing, communi-

cations, accounting), and using advanced technologies that are fit for purpose. A commitment to technical excellence reflects a culture that proactively enhances the quality of pharmaceutical products, processes, and services while promoting operational excellence within the organization.

Elements that may be addressed under this practice area include how effectively an establishment manages information across their organization to ensure data is attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available to all who need it regardless of the format (e.g., paper-based system, electronic system). The assessment may also review how effective an establishment is at synthesizing information from different sources, determining a proposed solution (e.g., technological upgrade of equipment or software) is fit for purpose, and ensuring effective implementation of the solution to enhance business operations or production processes.

Less mature establishments may struggle with data integration, which limits their ability to perform holistic reviews, gain a better understanding of their business operations, and identify emerging hazards to quality. This limitation can hinder their ability to identify opportunities for optimizing production operations or business processes. In contrast, more mature organizations have effective methods or mechanisms in place to maximize the use of relevant data and sources of knowledge, enabling them to optimize both production and business operations. Even when financial resources are available, less mature establishments may be resistant to embracing unfamiliar changes (e.g., technological, procedural, conceptual) that could enhance their business operations. Yet more mature establishments are early adopters and are willing to evaluate and accept changes that have been vetted and add value to their operations while controlling any other risks that are introduced via the changes.

5. Employee Engagement and Empowerment

Employee engagement refers to employees' motivation and commitment to positively impact an organization's quality policy and quality objectives. Engaged employees understand and care about how their roles within the organization impact patients and consumers, product quality, and product availability. Engaged employees at all levels take ownership and are empowered to identify, communicate, escalate, and initiate changes that continually improve processes, procedures, and practices.

Elements that may be addressed under this practice area include how willing employees are to making suggestions that can improve business or manufacturing operations and whether leadership creates an environment that encourages

employees to share their thoughts and ideas. The assessment would also gauge employees' understanding of the impact of their role on product quality and patient safety. Engaged employees will seek and have access to opportunities to grow their expertise and have clear career paths to grow within the organization.

Less mature organizations will miss out on opportunities to solicit feedback from employees and act upon their suggestions to improve quality systems and production processes. A workforce that is not engaged, empowered, and enthusiastic will struggle to continually complete routine duties in a reproducible manner with the highest standards, employee turnover may be high, and institutional knowledge may be lost as a result. Employees who do not understand the importance of their role in the organization and appreciate the responsibility they bear toward patients may not give their work the attention it needs. By contrast, more mature establishments will have effective methods to facilitate engagement with staff at all levels. Establishments that foster a culture of active participation without fear of reprisal can more effectively leverage the expertise, experience, and input of employees to drive continual improvement. Satisfied employees are more likely to go above and beyond the call of duty and stay with an organization, keeping institutional knowledge in-house. Employees who actively feel they are part of the organization will be more invested in their work and see it as an investment in themselves and the patients they serve.

Addressing Possible Misconceptions About the QMM Program

QMM assessments are not used to evaluate compliance with CGMP. CGMP requirements are foundational to any drug manufacturing operation. Compliance with CGMP is evaluated through surveillance inspections or other inspections conducted by credentialed investigators under section 704(a)[11] of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Inspections are mandatory and refusal to permit entry or inspection is prohibited under section 301(f)[12] of the FD&C Act. In contrast, QMM assessments are not part of FDA's inspection authority and participation in the QMM program is voluntary. The QMM assessment cannot be used to determine compliance with CGMP. QMM assessments focus on evaluating the behaviors, practices, and quality culture within an establishment. Higher levels of QMM indicate a higher

[11] 21 U.S.C. 374(a).

[12] 21 U.S.C. 331(f).

process capability and performance and a reduced risk of quality failures that can contribute to drug shortages.[13] [14] [15] [16]

QMM assesses manufacturing establishments; QMM does not evaluate product quality. QMM assessments cannot and do not evaluate the quality of specific products. FDA evaluates product quality throughout the lifecycle by assessing regulatory submissions, post-market quality defect reports (e.g., field alert reports, biological product deviation reports, MedWatch reports, consumer complaints), sampling and testing results, and through CGMP inspections.

Maturity is independent of establishment size or age, and the types or number of products produced. QMM assessments focus on evaluating if a culture of quality exists at the establishment and how this mindset is reflected in the quality practices employed. Therefore, these evaluations are not product-specific, and the maturity of an establishment is not dependent on factors like establishment size or age, and the types or number of products that are manufactured, tested, processed, packaged, labeled/re-labeled, or held. Simply having larger profit margins does not mean an establishment is highly mature. For example, establishments with greater financial resources that purchase state-of-the-art equipment may not be highly mature if their use of resources and technology is not fit for purpose and appropriately controlled. Rather, establishments with a highly mature quality culture use practices that invest time and resources commensurate with their financial resources to proactively improve their operations.

QMM assessments are distinct from the collection of Quality Metrics. Quality metrics (QM) are *quantitative* data that are collected and reviewed by establishments to determine the capability and effectiveness of manufacturing processes and systems. On the other hand, QMM assessments are *qualitative* and focus on approach, including understanding why establishments select and define specific metrics for monitoring and how they leverage data to drive continual improvement.

QMM is NOT an additional burden or requirement. It is, in fact, integral to an establishment's quality system. Most establishments already have processes and practices aligned with QMM. Achieving higher levels of QMM naturally results from an establishment's proactive continual improvement efforts. Investing in a culture of

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[13] L Yu and M Kopcha, 2017, The future of pharmaceutical quality and the path to get there, Int J Pharm, 528(1-2): 354-359.

[14] M Fellows, T Friedli, Y Li, J Maguire, N Rakala, M Ritz, M Bernasconi, M Seiss, N Stiber, M Swatek, and A Viehmann, 2022, Benchmarking the Quality Practices of Global Pharmaceutical Manufacturing to Advance Supply Chain Resilience, AAPS J, 24(111).

[15] U.S. Food and Drug Administration, Drug Shortages: Root Causes and Potential Solutions (Revised) (2020). Available at https://www.fda.gov/media/131130/download.

[16] European Medicines Agency, 2012, Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems, accessed August 21, 2023, https://www.ema.europa.eu/en/documents/other/reflection-paper-medicinal-product-supply-shortages-caused-manufacturing/good-manufacturing-practice-compliance-problems_en.pdf.

quality should not require the creation of new departments; a quality culture should be integral to the quality system. Moreover, the benefits of improving quality systems are well-known and can lead to long-term cost savings.[17] Each establishment makes decisions regarding how and where to invest resources, and this decision should consider the return on investment, not just the initial cost.

Conclusion

The QMM program seeks to promote a strong culture of quality, recognize establishments with robust quality management practices, and provide support and recommendations for areas where quality management practices can be enhanced. Through the program, industry participants and QMM assessors can work together to drive proactive continual improvement in the pharmaceutical industry.

The QMM prototype assessment protocol that CDER is developing will offer a structured, objective approach to evaluate an establishment's level of maturity in the five practice areas described in this paper. Management's commitment to quality sets the tone for the entire organization, ensuring that quality is prioritized, aligned with business objectives, and resourced appropriately. Business continuity ensures operational resiliency, safeguarding against disruptions and minimizing risks to the supply chain. An advanced PQS takes advantage of learnings gained across products and from all stages of the product lifecycle to optimize process performance and product quality. Technical excellence promotes the acquisition of new skills and the implementation of advanced manufacturing and analytical methods that are fit for purpose, driving operational excellence. Finally, employee engagement fosters a culture of quality throughout the organization, empowering employees to actively contribute to continual improvement and patient safety.

By focusing on these practice areas, the prototype assessment protocol will encourage establishments to embrace a holistic approach to quality management. The QMM assessment will identify areas of strength in quality management practices and provide recommendations for impactful growth opportunities. Through collaboration between industry participants and the QMM assessors, the prototype assessment protocol will help support the development of a shared understanding of a commitment to quality, ultimately leading to a more reliable drug supply and positive patient outcomes.

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[17] WE Deming, Out of the Crisis, 2018, Cambridge (MA): MIT Press.

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