05 December 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

via online submission to https://www.regulations.gov/

RE: [Docket No. FDA-2023-N-3721] "Quality Management Maturity Program for Drug Manufacturing Establishments; Establishment of a Public Docket; Request for Comments"

Dear Sir or Madam,

The International Society for Pharmaceutical Engineering (ISPE) is pleased to provide comments on the above-referenced document.

ISPE is a not-for-profit organization of individual members from pharmaceutical companies, contract manufacturing organizations, suppliers and service providers, and health authorities. The 20,000+ members of ISPE lead scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle in more than 90 countries around the world. ISPE does not take political positions or engage in lobbying activities or legislative agendas.

ISPE appreciates the opportunity to respond to FDA's questions on Quality Management Maturity (QMM). For nearly a decade, ISPE has played a leading role in the Quality Management Maturity dialogue, investing significant resources in pilot programs and other initiatives to develop a QMM program, titled Advancing Pharmaceutical Quality (APQ), to help industry not only assess but improve the effectiveness of their Pharmaceutical Quality Systems.

ISPE's comments are attached for your consideration. Please do not hesitate to contact me if you have any questions.

Respectfully,

Thomas B. Hartman
ISPE President and CEO
thartman@ispe.org
cc: Scott Billman, ISPE Board Chair

ISPE Response to [Docket No. FDA-2023-N-3721) "Quality Management Maturity Program for Drug Manufacturing Establishments; Establishment of a Public Docket; Request for Comments"

I. Overall Comment

ISPE is aligned with FDA's position that advancing quality is a benefit for all and sees value in a Quality Management Maturity (QMM) program and has thus developed the ISPE Advancing Pharmaceutical Quality (APQ) Program as an industry-led approach to foster proactive continual improvement. The APQ program is a voluntary, industry-led program for QMM based upon international ICH Q10 standards whereby industry can assess, aspire, act, and advance their level of QMM and share it independently with patients, consumers, customers, and health authorities globally. The appendix included with these comments provides detailed parameters for the APQ Program for reference.

As described in the following comments, ISPE believes that QMM programs have value to FDA, industry, and patients, regardless of industry-led or regulator-led. However, ISPE has concerns about proposals for an FDA-initiated QMM program. Without concrete regulatory incentives, manufacturers may shy away from a regulator-led program, reducing the program's reach and effectiveness. Furthermore, public sharing of QMM ratings could be misinterpreted and lead to undesired consequences, which could also deter manufacturers from joining a voluntary QMM program.

II. Addressing Docket Questions:

1. ***If you are a manufacturer, please identify the types of drug(s) produced in your establishment (e.g., active pharmaceutical ingredients, innovator drugs, innovator biologics, generics, biosimilars, or OTC monograph drugs). If you are not a manufacturer, please specify whether you are a purchaser, payor, pharmacy, healthcare provider, patient, regulator, supplier, distributor, contract service provider, or other (please describe).***

ISPE is a not-for-profit organization of individual members from pharmaceutical companies, contract manufacturing organizations, suppliers and service providers, and health authorities. The 20,000+ members of ISPE lead scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle in more than 90 countries around the world.

The ISPE Advancing Pharmaceutical Quality Team has expertise in developing a robust QMM Program, has led QMM pilots, collaborated with regulators, industry, and academia, and has led Quality Metrics studies for more than ten years. The team has a vested interest in helping manufacturers to improve QMM within their organizations.

2. ***What advantages do you anticipate that your sector (i.e., your organization and others like yours) would gain from CDER's voluntary QMM program?***

There are clear benefits to be gained when a company looks to enhance its quality management system and cultural excellence. ISPE believes the core goals of a QMM program are important and that

implementing QMM practices will foster a strong quality culture, provide opportunities to identify areas for growth, and help companies strive for continual improvement of quality management practice.

However, it is difficult to see the advantages of participation in an FDA based program for companies already participating in an industry-led or internal program. While there are significant benefits to advancing quality as an industry, this can be accomplished in a multitude of ways. Without clear regulatory incentives, industry may not see the advantage in utilizing the FDA program over other industry or site-established programs. A site-driven program utilizing an industry-led framework allows for a focused effort without the potential unintended consequences or barriers outlined in our response to question 5 below.

3. How would participation in a QMM program benefit you or your specific organization?

Please refer to our response to question 2 above.

4. How would you use information from a QMM assessment if it were provided to your organization? For example, if your organization acts as a supplier or contract organization, would you consider sharing information from a QMM assessment with a potential client? If your organization enters into contracts with purchasers, would you consider sharing information from a QMM assessment with a purchaser? If your organization is a purchaser, would you consider requesting information from a QMM assessment?

Information from a QMM assessment could be used by any individual establishment internally to identify focus areas for capital investment, training, and cultural improvements, or externally when establishing new relationships with potential customers and partners. The advantages of sharing outcomes of a QMM assessment in existing relationships could be limited since quality/technical agreements and supplier audits are already in place to ensure appropriate information is shared where deemed necessary.

From a pharmaceutical manufacturer's perspective, sharing information from a QMM assessment with a purchaser is not desired as it is not a replacement for cGMP requirements and should not be considered as such. As discussed further in our response to question 5, we do not envision advantages to making information on outcomes of a QMM assessment available to purchasers.

ISPE acknowledges that one objective of the FDA QMM program is to improve assurance of continued product supply and hence, mitigate drug shortages. While there are numerous factors that contribute to drug shortages, ISPE believes that it would be beneficial to conduct additional research to establish a correlation between the reduction of drug shortages and the implementation of a QMM program. By exploring this relationship, we can gain a better understanding of how QMM programs can be leveraged to mitigate the impact of drug shortages and ensure that patients have access to the medications they need. ISPE requests that data that directly correlates drug shortages to QMM be made available.

5. What, if any, unintended consequences, roadblocks, or other concerns do you anticipate with a voluntary QMM program? What barriers to participation do you anticipate? Please explain. Which of these unintended consequences might be unique to stakeholders like you? Why?

While ISPE understands that it is not the FDA's intention, there is a concern that the QMM rating/output could potentially be misinterpreted as a rating of *product* quality, which could lead to misinformation, promote patient aversion, fear, lead to medication/pharmaceutical product compliance issues, decrease public confidence in manufacturers, and result in unmerited bias against specific manufacturing regions or sectors (e.g., OTC, generics). Additionally, sharing the rating/output with the public may lead to misinterpretation leading to poor conclusions and decisions.

Furthermore, there may be unintended barriers to the FDA's QMM program. Many companies already employ comprehensive quality maturity programs that drive continual improvement which could reduce the incentive to participate in the FDA QMM program. Internal or industry programs offer an alternative to a regulator-driven program; these programs do not have an external visibility element of a regulator-driven program and the assessment can be tailored to focus on relevant improvement areas, time and preparedness for cross-functional assessment, and control burden/resource challenges. Participating in an industry program can also provide benefits such as greater flexibility in managing overall priorities and timelines.

Manufacturers also could have concerns about the potential impact of QMM results on FDA actions or liability, particularly if publicly shared.

As already mentioned, ISPE acknowledges that one objective of the FDA QMM program is to improve assurance of continued product supply and hence, mitigate drug shortages but cautions that the program could also negatively impact supply. A QMM rating shared with purchasers could shift purchasers to wanting to work with specific suppliers with a higher rating and avoid other suppliers, which could lead to the higher-performing suppliers not being able to meet market demand.

6. FDA anticipates that each establishment would be provided with a detailed report following their QMM assessment. What would you want such a report to contain?

The QMM Assessment report should provide a comprehensive analysis of the practice areas including:

A. A comprehensive overview outlining both the strengths of the organization and the areas requiring improvement.
B. A viable strategy or specific actions that may effectively drive improvement, presenting clear and actionable recommendations for enhancing quality management practices. It remains at the discretion of the company to decide which actions to take for improvement.
C. The overall rating resulting from the in-depth analysis of the assessment criteria, which will reflect the organization's maturity in each of the practice areas.
D. Year-over-year trend analysis with demonstrated improvement for a manufacturer's site.

E. A blinded benchmark across the industry participants, conducting a comparative analysis of organizational performance in each of the five practice areas while maintaining confidentiality and anonymity regarding the specific companies involved.

It is crucial for the assessors to establish effective follow-up from a QMM assessment to clarify the report, create a sense of partnership, and demonstrate the FDA's commitment to ongoing improvement.

Additionally, FDA 'credit' and incentives for demonstrated evidence of robust industry-based QMM programs. Furthermore, investigators could document evidence of an Advanced Pharmaceutical Quality system within the manufacturer's EIRs per FDA Program 7356.002, Attachment B, "Examples of Indicators of an Advanced Quality System."

7. With respect to the outcomes of a QMM assessment, what are your thoughts about making outcomes public? Would your thoughts be different if the outcomes were generally qualitative (e.g., descriptive information) versus quantitative (e.g., a numerical rating)?

As mentioned in response 5, ISPE does not recommend that the output of the QMM program be shared publicly due to the risk of misinterpretation as a rating of product quality, potential negative impact on drug supply, or poor conclusions or decisions made by the public. Public misperception of a QMM outcome could lead to shortages if purchasers do not work with suppliers having lesser outcomes than a competitor (skepticism of partnering with certain companies). There is also a high level of concern regarding scoring and sharing data with buyers and others who may use the data without the proper understanding/context to drive business decisions. Furthermore, there could be fear about the legal liability of the information. If the outcomes of a QMM assessment are explicitly publicized, the outcomes may raise expectations, and failure to meet those expectations can lead to reputational damage. Despite the Agency's best intentions, making scores available to different stakeholders could foster poor behaviors (e.g., decision-making based on ratings and possibly contrary to product supply continuity improvements).

If data outcomes from the QMM assessments are to be shared, they should only be distributed to those companies participating in the QMM program and provided in a blinded fashion so as not to discriminate the data from any specific company of origin.

While quantitative scores can provide a more structured approach to assessing QMM, a qualitative, descriptive approach could offer greater flexibility in capturing the nuances of an organization's quality management practices. However, it is important to note that ISPE still advises against making the outcomes of the QMM assessment public, regardless of the approach used to avoid potential misinterpretation of the results.

8. What other feedback would you like the FDA to consider for a voluntary QMM program?

With a voluntary FDA QMM program, the FDA should consider clear incentives for industry to participate, like those offered by CDRH Voluntary Improvement Program. Incentives could include:

- Pre-announced surveillance inspections
- Reduced surveillance inspection frequency
- Shorter time and/or less information for post-approval changes
- Reduced review timelines and/or reduced submission content for changes
- More streamlined and targeted inspections, in-person or remote
- PAI and PLI waivers
- Site inspection decisions that include consideration of industry-developed programs, (when voluntarily shared)
- Provide 'credit' and incentives for demonstrated evidence of robust industry-based QMM programs
- Documented evidence of an Advanced Pharmaceutical Quality system within manufacturer's EIRs per FDA Program 7356.002, Attachment B, Examples of Indicators of an Advanced Quality System
- Access to FDA consultation / best practice benchmarking in the QMM program areas

Other Considerations:

- The proposed FDA practice areas should focus on elements related to an establishment's Cultural Excellence, including the incorporation of key behavioral indicators into the performance management process. A diverse set of assessment criteria should be considered when working to establish trusted partnerships and enhance quality maturity across cultural contexts.
- Based on ISPE's experience in developing the APQ Program, it is recommended to adopt a phased approach to implementation. As an example, focus on the development/implementation of one practice area, applying the learnings, and then expanding the program to the next practice area.
- Any QMM program must support all pharmaceutical business models from less mature small start-ups to large, mature corporations.
- Advanced technology does not equal improved quality. Quality can be strong without AI, continuous manufacturing, etc. Industry would appreciate one blended program from FDA Centers – for example with CDRH Voluntary Improvement Program.
- FDA to provide the algorithm used for assessing the information fosters understanding among stakeholders, enhances accountability, and ensures that the evaluation process is conducted with the utmost objectivity, transparency, and clarity.

ISPE remains ready to engage with FDA and industry to advance and develop a meaningful and beneficial QMM program. This approach would align with CDRH's Voluntary Improvement Program (VIP) which is primarily facilitated by industry. As described in the CDRH draft guidance, *Fostering Medical Device Improvement: FDA Activities and Engagement with the Voluntary Improvement Program*, the VIP program offers participating manufacturing sites potential benefits including enhanced risk-based inspection decisions, reduced review timelines, and/or reduced submission content for changes. Clearly articulated potential incentives are essential for a successful QMM program for drugs, as FDA indicated in the 2022 *OPQ White Paper*.

Achieving a successful QMM program could help fulfill FDA's vision of Pharmaceutical Quality for the 21st Century of a *"maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drugs without extensive regulatory oversight."*

References

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3. An Office of Pharmaceutical Quality (OPQ) White Paper, Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals, 2022. Available from https://www.fda.gov/media/157432/download
4. Quality Management Maturity for Finished Dosage Forms Pilot Program for Domestic Drug Product Manufacturers; Program Announcement, FRN, October 16, 2020. Available from https://www.federalregister.gov/documents/2020/10/16/2020-22976/quality-management-maturity-for-finished-dosage-forms-pilot-program-for-domestic-drug-product
5. Quality Management Maturity for Active Pharmaceutical Ingredients Pilot Program for Foreign Facilities; Program Announcement, FRN, October 16, 2021. Available from https://www.federalregister.gov/documents/2020/10/16/2020-22977/quality-management-maturity-for-active-pharmaceutical-ingredients-pilot-program-for-foreign
6. FDA CDRH draft guidance Fostering Medical Device Improvement: FDA Activities and Engagement with the Voluntary Improvement Program, May 6, 2022. Available from https://www.fda.gov/media/158180/download

Appendix: ISPE Advancing Pharmaceutical Quality (APQ) Program

ISPE is aligned with FDA's vision of the value of QMM and initiated the ISPE Advancing Pharmaceutical Quality (APQ) program in 2018 as an industry-led approach to advance pharmaceutical quality. The basic framework of the APQ program is to "assess, aspire, act and advance" quality maturity and was outlined in ISPE's comments to the FDA dockets in 2018.

The APQ program provides a framework for assessing and enhancing the effectiveness of the Pharmaceutical Quality System (PQS) as described in ICH Q10.

The APQ program:

- Recognizes that the ability to advance quality management maturity lies within the industry itself (developed by industry representatives for use by industry)
- Builds upon the ICH Q10 model and enhances the PQS elements with the aspects of cultural excellence, operational excellence (OPEX), knowledge management, and continual improvement
- Provides a comprehensive approach for assessing and improving an organization's quality management maturity to advance the state of quality within the organization

The APQ program focuses on eight overarching goals:

1. Integrate quality management maturity, cultural, and operational excellence principles, tools, and approaches
2. Support and incentivize continual improvement
3. Foster industry ownership of quality beyond compliance
4. Promote effective and efficient use of resources
5. Encourage self-improvement and supplier improvement
6. Enable structured benchmarking, knowledge sharing, and learning among organizations
7. Increase the reliability of supply for quality products
8. Offer routes to delivering sustainable competitive advantage

At the core of the APQ Program is the Assess, Aspire, Act and Advance framework which provides a set of tools, resources, and systematic approaches for organizations to advance the maturity and effectiveness of their PQS. The program consists of five Good Practice Guides which are described below.

The ISPE Advancing Pharmaceutical Quality, Quality Management Maturity Program includes Five Guidance documents:

1. The first ISPE APQ guide is Corrective Action & Preventive Action (CAPA) System. ICH Q10 demonstrates defined requirements for a robust corrective action and preventive action system throughout the product lifecycle.

The ISPE CAPA guide covers the practical application of the APQ framework for each CAPA system requirement by evaluating the following elements:

- CAPA Documentation
- Problem Identification
- Root Cause Identification
- Corrective and/or Preventive Actions
- CAPA Effectiveness
- CAPA Metrics
- Governance, Management Oversight, and CAPA Prioritization

2. The second ISPE APQ guide is Change Management System. ICH Q10 establishes clear guidance for the effective management of change throughout the product lifecycle which enables quality improvement and is critical to patient safety, supply reliability, as well as operational effectiveness and efficiency.

   This ISPE Change Management Guide provides a quality management framework for assessing and advancing Change Management system maturity level by evaluating:

   - Change Management Documentation
   - Change/Scope Identification
   - Change Rationale, Impact/Level, and Risk
   - Change Plan/Execution
   - Post-Change Evaluation
   - Change Management Metrics
   - Governance, Management Oversight, and Change Management Prioritization

3. The third ISPE APQ guide is Management Responsibilities and Management Review. ICH Q10 sets a clear expectation regarding the role of strong leadership in terms of demonstrating and communicating “strong and visible support for the pharmaceutical quality system.”

   The ISPE Management Responsibilities and Management Review provides a quality management framework for assessing and advancing leadership systems. It provides a systematic and proactive approach to evaluating management responsibilities and key leadership components by evaluating the following elements:

   - Patient/Consumer Focus
   - Management Commitment
   - Quality Planning
   - Internal Communication
   - Management of Outsourced Activities and Purchased Materials
   - Management of Change in Product Ownership
   - Regulatory and Industry Awareness

4. The fourth ISPE APQ guide is Process Performance and Product Quality Monitoring System or PP&PQMS. ICH Q10 establishes an expectation for pharmaceutical companies to "plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained."

   This guide ISPE provides a quality management framework for assessing and advancing an organization's PP&PQMS maturity level by evaluating the following elements:

   - Establishing a Control Strategy
   - Determining Tools for Measurement and Analysis of Parameters and Attributes
   - Analyzing Parameters and Attributes
   - Identifying Sources of Variation
   - Including Feedback on Product Quality from Internal and External Sources
   - Providing Knowledge to Enhance Process Understanding

5. The fifth ISPE APQ guide is Cultural Excellence. The Cultural Excellence Guide shares insights on quality culture improvement across six key dimensions and outlines practical and powerful approaches, practices, and tools to support the implementation of the cultural excellence framework and promote behavioral change that will ultimately benefit the patient and the business. It is based upon the 2017 ISPE Cultural Excellence report with enhanced features supporting key behavior assessment at employee and management levels, a robust recognition and reward program, and third-party contract evaluation. It provides a quality management framework for assessing and advancing Cultural Excellence maturity by evaluating the following elements:

   - Leadership and Vision
   - Mindsets and Attitudes
   - Gemba and Employee Engagement
   - Leading Quality Indicators with Metrics that Matter
   - Proactive Management Oversight, Review and Reporting
   - Cultural Enablers