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

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

Dear Madam or Sir,

PDA appreciates the opportunity to provide feedback to the FDA as the agency develops and establishes a voluntary Quality Management Maturity Program to incentivize investments in mature quality management practices. In our attached comments, PDA offers specific comments and feedback that we believe will be helpful in the further development of this program.

PDA is a non-profit international professional association of more than 10,000 individual members scientists having an interest in fields of pharmaceutical, biological, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in quality systems, quality management, quality culture, and quality metrics on behalf of PDA's Regulatory Affairs and Quality Advisory Board.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,

Glenn Wright
President and CEO

cc. Josh Eaton, PDA; Carrie Horton, PDA; Danielle Bretz, PDA

Responses to "FDA Quality Management Maturity Program for Drug Manufacturing Establishments, Request for Comments."

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).

These comments are on behalf of PDA, a non-profit international professional association of more than 10,000 individual member scientists interested in pharmaceutical, biological, device manufacturing, and quality. PDA members work at all the establishment types mentioned in the question plus at CMOs as well as with vendors supplying manufacturing equipment, materials, and services. Our comments have been prepared by a task force of PDA members with expertise in quality systems, quality management, quality culture, and quality metrics on behalf of PDA's Regulatory Affairs and Quality Advisory Board.

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?

i. QMM can be an additional data point that companies can use in their continuous improvement programs. It also provides small companies/those with fewer resources a roadmap to develop their own formal quality maturity program.

ii. The FDA's QMM program could serve as the best practice and industry benchmark for measuring maturity of quality systems with the following important advantages:
   a. Standardize how the industry assesses operational excellence
   b. Increase the "industry standards" beyond only meeting cGMP compliance requirements
   c. Validate current continuous improvement efforts (i.e., provide effectiveness checks for continuous improvement-focused initiatives)
   d. Allow for benchmarking across establishments that participate against aggregate results made available publicly or at least to those establishments that participate

iii. As shared in the Office of Pharmaceutical Quality's (OPQ) QMM White Paper, it is valuable for the pharmaceutical industry, especially in the generic sector where medicines have comparable, if not identical, efficacy and safety, to establish another method of differentiating products for purchasers. As economics will favor the lowest cost option this creates a perverse incentive not to invest in the highest quality systems and processes. Therefore, a robust education program will be needed in order to incentivize the purchase of products with more robust supply chains and more mature quality systems which may be delivered at a slightly higher cost. With enough participation and transparency to the aggregated results, manufacturers who adopt a QMM program could see the following advantages:
   a. Positive public recognition for companies that have a lower risk for supply chain interruptions due to their robust QMM maturity
   b. The opportunity to use the FDA QMM program across the board in lieu of retailer quality programs (e.g., Global Retailer and Manufacturer Alliance (GRMA))

c. Consultation and/or education from the FDA on improving areas that have gaps as identified by the assessment
d. The FDA QMM program helps in systematically improving processes, leading to higher-quality products or services.
e. Efficient processes and reduced errors can lead to cost savings over time.
f. A mature quality management system is likely to include robust risk management practices, helping the organization identify and mitigate risks proactively.

Note: All advantages are predicated on transparency in the QMM participation and results.

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

PDA recommends several benefits of participation in a QMM program that are preventive in nature. These include intangible as well as tangible benefits. Many poor-quality issues are avoided when a company adopts and follows a QMM program, leading to an overall decrease in the cost of quality. Benefits include but are not limited to robust quality improvement culture and increased regulatory compliance. Moreover, sites that invest in QMM can be expected to see increased operational efficiency and improved manufacturing processes.

When Quality Culture improves, it drives better communication and builds a more robust continuous improvement culture. Ideally, this leads to supply chain reliability, market recognition, and a stronger competitive advantage, which builds consumer trust and benefits to patients. If the economics of medicines in the U.S. were truly market-driven, this relationship between cost and value would be more directly realized.

The QMM program could support better interactions and decision-making between MAH and external service providers if disclosure of QMM status with the FDA or the requirement to conduct QMM assessments is built into quality agreements. Benchmarking across specific industry sectors could be used to better understand CMO/CDMOs, suppliers, capabilities, and continuous improvement efforts if these details are shared with authorized business partners. PDA recommends that the FDA provide visibility into site maturity and not information tied to specific products. CMOs and suppliers would have similar positive Quality Culture benefits as listed above from the QMM program, increasing the confidence levels for MAHs in partnership decisions (e.g., name recognition and reputation). Better quality equals a better bottom line, and this economic benefit should not be underestimated, although it does not appear on a balance sheet. Here is one example How Quality Impacts Your Bottom Line (smartbear.com)

Potential benefits for CMO/CDMO participation in the FDA QMM program may include a decreased risk profile for fewer or waived inspections, pre-announced inspections so that specific product/MAH manufacturing activities/visits may be scheduled, and/or remote inspections that could be scheduled with both MAH/CDMO participating simultaneously.

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 the QMM assessment output can be leveraged both internally and externally. Internally, the assessed can use the report to identify areas for improvement in practice areas and their respective elements. This approach would assist organizations that may be resource-constrained in obtaining an additional objective assessment. We encourage this behavior as it reinforces continuous improvement within an organization and fosters an environment of collaboration.

PDA recommends suppliers and contract organizations sharing site QMM assessment results with potential business partners, which may provide a competitive edge for a supplier or contract organization. It showcases a higher level of quality management maturity, fostering trust and confidence among potential clients. This level of transparency and commitment to quality can differentiate an organization in a competitive market. From a buyer's perspective, it confirms a buyer's decision to reach out to the CMO or supplier to engage in business-related activities.

For a manufacturing organization, one could externally use the QMM assessment output when evaluating another entity (the assessed) for potential partnership, whether it is sending their QMM output or receiving the other entity's QMM output. Having a systematic and objective approach to evaluating different stakeholders is extremely valuable. These reports would allow an organization (the purchasers) to review future ventures (potentially assessed entities) with the benefit of the assessed site's output, minimizing inherent bias.

Engaging with purchasers, the information from a QMM assessment could be beneficial during contract negotiations. It illustrates the organization's dedication to maintaining high-quality standards, which could facilitate long-term relationships by establishing a foundation of trust and quality assurance.

It is understood that a single rating of an establishment may influence a buyer's decision when reviewing potential contracts. However, we want to emphasize that a risk and vulnerability assessment of supply continuity is a multifaceted exercise that must evaluate the company's suppliers and its manufacturing/warehousing operations. Therefore, contextual information about each establishment's QMM rating is critical. Ideally, this ensures that the purchaser gains comprehensive, valuable data when making decisions that best meet their needs.

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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?

There are several potential unintended consequences related to the implementation of a voluntary QMM program, as follows:

i. **Voluntary Participation**: Not all organizations may opt-in, potentially creating a divide in quality standards across the industry. Changing economics, including incentives, to value participation will be key to overcoming this barrier.

ii. **Resource Allocation**: Meeting QMM standards may require increased or substantial investment in terms of time, personnel, and finances, which could deter participation. Companies may perceive this as just one more layer of requirements to meet. Smaller organizations that are unable to support the resource investment may have challenges obtaining contracts if their customers start to require QMM assessment results. There must be economic benefits of participation to balance the investments.

iii. **Consideration for Generics**: Generic manufacturers who operate with slim margins may be unintentionally forced to exit the market to avoid having poor QMM results, potentially exacerbating or causing a drug shortage.

iv. **Program Naming**: As the program's name is "Quality" Management Maturity, it may be perceived by companies as an initiative that should be the responsibility or owned by the Quality department instead of driving the cross-functional ownership and engagement needed to ensure the objective of preventing drug shortages. The name of the program may have the unintended consequence of promoting it as a compliance program. PDA recommends a focus to ensure the goal of the program is clear such as "QMM **to Ensure** Supply Chain Resiliency"

v. **Program Objective**: There is a potential that stakeholders will misinterpret the FDA's QMM ratings as being about product quality as opposed to its stated objective of being about preventing drug shortage. During the seminar the FDA held in May 2022, the stakeholders on the call repeatedly confused the QMM rating as being about product quality rather than supply continuity. Speakers at the November Advisory Committee also seemed to link strong QMM to product quality. This confusion may cause unnecessary concern among end-users or patient groups that their medications are in some way substandard based on the QMM rating of the manufacturer.

vi. **Feedback Loop**: Assessment results without commentary may not be as meaningful to the end-user or fair to the company being assessed. However, sharing commentary behind the ratings may inadvertently expose proprietary information.

vii. **Complex Technologies**: Companies may feel pressure to move away from complex technologies, such as sterile manufacturing because it could be more challenging to achieve a high QMM score. This perception could unintentionally lead to increasing drug shortages for parenteral generic products, which are currently a large part of the problem or could result in a lack of development of generic products with more complex modalities.

PDA representatives also perceive several potential roadblocks to the successful implementation of the FDA's voluntary QMM program, including:

i. **Consistency in Assessment**: Ensuring fair and consistent assessments across various organizations may be challenging, possibly affecting the program's credibility.

ii. **Data Privacy**: Sharing assessment results could raise concerns regarding data privacy, proprietary information, and competition, potentially impacting willingness to participate.

iii. **Perceived Value**: Organizations might question the perceived value or return on investment of participating in the program, especially in the absence of mandatory participation.

iv. **Technical Expertise**: The lack of necessary technical expertise to meet the QMM standards could be a barrier for some organizations.

v. **Industry Awareness**: A lack of awareness or understanding of the QMM program and its benefits could hinder participation.

vi. **Fear of Negative Outcomes**: Concern over potential adverse outcomes, such as uncovering non-compliance issues, might deter participation. The FDA has provided instructions that a maturity assessment is not compliance related. However, there is industry concern that any compliance issue (e.g., a recall of a failed cGMP inspection) would immediately drop the QMM score, which would conflate the two concepts. Additionally, the results of a negative inspection are not public until a Warning Letter is issued. Therefore, any immediate impact on a QMM score could preempt this disclosure process.

vii. **Timeliness of Assessments:** Concern that the FDA will not be able to complete reassessments in a timely manner, thus leaving a poor result in the system after conditions at the site have improved. PDA recommends an option for more timely updates would be to allow the participating body to submit a self-assessment to the FDA QMM dataset that would be clearly flagged as such. This could be replaced by the next official FDA QMM assessment in time.

Each of these concerns and barriers could affect stakeholders differently. For instance, smaller entities might find the resource allocation more burdensome compared to larger organizations. Similarly, data privacy concerns might be more pronounced for entities with proprietary processes or competitive advantages at stake.

Additionally, there are several other general concerns that need review and clarification prior to the successful implementation of this program, including:

i. It is unclear how or if a single QMM rating will be applied to a product with a complex supply chain and/or how that will be communicated to stakeholders. Supply reliability is multifaceted and depends on each party's reliability in the supply chain, the robustness of supply risk management programs, and continuous market monitoring. In addition, since supply chain reliability is dependent on organizations not currently or typically evaluated by the Agency, it is unclear how accurate or comprehensive a QMM rating will be in assessing supply chain reliability.

ii. There is a concern that the rating system will be used as part of the risk-based approach to inspection frequency, which will deter aging facilities and generics manufacturers from participating. These are key participants in driving the reduction of drug shortages.

iii. As this program starts, some sites and companies may want to participate in the QMM assessment but are not ready to disclose the results. Potential partners may question why a company is not disclosing their participation and assume, based on this statement in the QMM white paper, that they are not meeting basic compliance standards: "In practice, the ability to assign even the lowest QMM rating implies that a manufacturing site at least complies with minimum regulatory standards" (page 11). To ease this concern, PDA recommends having a public website that gives the status of companies as non-participating, pending, accepted, or not accepted into the QMM program. This simple level of information would be valuable to other companies wishing to understand the status of a potential business partner or supplier.

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 serve as a valuable tool for organizations, enabling them to pinpoint areas for continual improvement. The report would be expected to include an in-depth examination of the five practice areas described in the paper "CDER's Quality Management Maturity (QMM) Program: Practice Areas and Prototype Assessment Protocol Development." The QMM Assessment report should include:

i. **Quantitative Assessment**: A structured rating system should be applied, and evidence, data, and analysis supporting the assessment findings should be included. PDA recommends the FDA disclose the algorithm employed to assess this information, ensuring clarity and objectivity in the rating process. Over the life of the program, it is essential to provide a benchmark by comparing the current Quality Maturity scores with data from previous years, enabling organizations to track their progress. Furthermore, these scores should be benchmarked against establishments of a similar nature, allowing for meaningful comparison and insights into relative performance within the industry. This quantitative assessment offers a data-driven approach to continual improvement based on the benchmarked data and past performance.

ii. **Qualitative Assessment**: In addition to quantitative measures, qualitative indicators for continual improvement play a crucial role in providing insights that guide the organization toward enhanced quality maturity. These indicators serve as invaluable sources of feedback, empowering the organization to make informed decisions, establish clear goals, and monitor the evolution of its quality maturity over time. A comprehensive qualitative assessment should include positive and negative examples to shed light on the context behind the ratings. By presenting these examples, the organization will gain a well-rounded understanding of its strengths and weaknesses, facilitating the identification of specific areas for continual improvement.

Here is an example of what a QMM Assessment Report could contain:

Executive Summary:	An overview that encapsulates the key findings, ratings, and recommendations from the assessment.
Rating:	The overall rating awarded is based on the assessment criteria, showing the organization's level of quality management maturity.
Strengths and Weaknesses:	Detailed analysis of areas where the organization excels and areas requiring improvement.
Recommendations:	Specific, actionable recommendations for enhancing quality management practices.
Detailed Findings by Practice Area:	In-depth analysis and scoring in each of the five practice areas assessed.
Benchmarking Data:	Comparative data showing how the organization fares against industry standards or peers.

Action Plan:	A proposed roadmap for addressing identified gaps and advancing quality management maturity.
Supporting Documentation:	Evidence, data, and analysis supporting the assessment findings.
Feedback Mechanism:	A means for the organization to provide feedback on the assessment process and findings.
Follow-Up Procedures:	Information on any follow-up assessments, support resources, or other next steps.
Contact Information:	Contact details for the assessment team or relevant personnel for further discussion and clarification.
Appendices:	Additional data, charts, graphs, or other relevant information.

In addition to providing a report, PDA recommends the FDA consider facilitating collaborative feedback sessions and creating a platform where sites can engage in open dialogue, seek clarifications, and exchange information. This approach fosters a collaborative environment for effective action plan development. This approach enhances transparency and promotes a sense of partnership and shared responsibility in the pursuit of continuous quality improvement.

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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)?

PDA agrees with the FDA's intention to use the concepts of quality system maturity to create an economic incentive for investment in reliable quality systems. In order to change the behavior of purchasers or formulary decision makers, some type of disclosure of assessment outcomes will be needed. As has been demonstrated through academic research by Anthony Sardella at the Olin Business School at Washington University and others, one of the primary underlying causes of drug shortages is economic, Additional support for the economic challenges as a basis for shortages is the IQVIA Institute for Human Data Science Nov 2023, *Drug Shortages in the U.S. 2023 A CLOSER LOOK AT VOLUME AND PRICE DYNAMIC*, which states "shortages are more common at lower prices." This would apply to approximately 56% of molecules in shortage priced less than $1.00 per unit, where competition may be driving some of these drugs below their cost of production and distribution, causing manufacturers to exit the market and disincentivizing new entrants.

However, challenges remain with disclosure of the QMM program results. While a positive QMM assessment or rating may afford the participating body a solid reputation, a negative one is more likely to impact its competitiveness. Additionally, public misconception of a QMM rating could lead to shortages if purchasers refuse to engage with suppliers below a certain rating. PDA recommends that the FDA address the following considerations regarding disclosure:

i. **Transparency vs. Privacy**: Balancing transparency and privacy is crucial. Establish a clear policy on what gets disclosed and ensure organizations are well-informed. Implement a secure system for the participating body to state who can access their QMM assessment information. Be clear on the frequency with which ratings will be issued or updated or whether there will be any process to appeal or amend the rating.
ii. **Qualitative vs. Quantitative Disclosure**: Qualitative data offers context but might be subjective, while quantitative data provides objectivity but might lack nuance. A balanced approach combining both could be more informative and fairer than choosing a single approach.
iii. **Stakeholder Engagement**: Engage with stakeholders to understand their concerns and preferences regarding disclosure. Their input can provide valuable insights.
iv. **Educational Support**: Offer educational resources to help the public and stakeholders understand the assessment outcomes and their implications.
v. **Feedback Loop**: Establish a feedback mechanism to continually improve the disclosure process based on stakeholder input and evolving industry standards.
vi. **Trial Period**: Consider a trial period for the disclosure policy, allowing for adjustments based on feedback before full implementation.
vii. **Competitive Concerns**: The assessment must address concerns about competitiveness by ensuring fair, consistent assessment and disclosure practices.
viii. **Legal and Regulatory Framework**: Provide a clear disclosure policy that aligns with legal and regulatory frameworks to mitigate legal risks and ensure compliance.
ix. **General Public Accessibility to Results:** Given that the public and patients have almost no representation in purchasing decisions of their medicines, we propose that any public disclosure, including academic, media, or other governmental institutions (OMB, Congress, etc.), would be an aggregate of scores and qualitative results perhaps by sector, by geography or by product type. Consolidated results by sector or product type could be shared more broadly, including to the public. PDA recommends these results or scores could be managed similarly to ISO certification, where each company can choose to undergo an assessment and then decide to advertise the results. However, firms are less likely to participate if participation is highly costly. This aggregated information would be fully available through Freedom of Information Act requests.

PDA offers one example of how QMM assessment report disclosure could be managed in a secure fashion. The QMM results could be shared in a similar way that DMF information, which is also commercially sensitive, is managed today. The FDA would release the QMM assessment results of a site to purchasers, hospital systems, Medicare, or suppliers who have a letter of authorization from the assessed site granting the FDA the ability to release the results. A firm would have the option and economic incentive to grant broad access or restrict access to the assessment results as they would like, based on what letter was on file with the FDA. Using current technology, this would not rely on physical letters. However, there could be a portal where companies enable the authorization with a key provided to the FDA to unlock the available ratings to a designated recipient. This authorization could perhaps rely on Blockchain or other encryption to protect unintentional disclosure and track who was accessing the information.

With the implementation of a letter of authorization (LOA) type approach, the FDA can provide each assessed site/company with the decision rights on the publication of their individual QMM rating.

Manufacturers could choose to disclose their FDA rating/results to potential customers and/or purchasers at their discretion. This would then become a component of the normal contracting process and one of several factors considered, providing the flexibility for different purchasers to weigh factors differently while allowing the companies to maintain control of the information flow. Allowing a site/company some experience with the assessment outcomes before having the results disclosed would incent participation as it lowers the reputational risk. This could be for CMOs/suppliers sharing ratings with prospective business partners as well as drug product manufacturers sharing ratings with purchasers.

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

While industry and the FDA have been discussing and developing metrics approaches and now quality management maturity models over the last ten years, advancements in data analytics and artificial intelligence have advanced tremendously. The ongoing development of alternative approaches to predicting conditions likely to lead to a site quality issue or to increase the risk of a market interruption will likely outpace the use of QMM assessments as currently envisioned.

The Office of Quality Surveillance (OQS) now has data analytics tools and models based on a large set of internal and public information about the pharmaceutical catalog of sites which supply medicines to the US Market with the ability to deliver a risk-based inspection model. Private entities have also developed predictive algorithms that are or will soon be commercially available which also predict the sites with conditions likely to lead to quality problems and potential supply interruptions. This application of advanced analytics and artificial intelligence will always be current, easily adjusted for new data sources, objective or at minimum have the same bias across the entire data set and will require few human resources to maintain. The advantages of these models will drive parties interested in using quality parameters in decisions to purchase their information or subscribe to a continual feed of data rather than rely on manual, intermittent, and human dependent execution of quality maturity assessments as currently envisioned in industry and as the FDA develops these models.

PDA suggests making contracting and purchasing decisions based on data-based model outputs and algorithms will be simpler and more predictive. If the overall goal is to enable the marketplace to pay more based on the knowledge of which firms and sites are most likely to have reliable supply chains and sustainable quality systems, the use of commercially available standard algorithms or data sets or the sharing of the FDA's internal data analytics results is likely to be the most viable path forward.

The FDA could have the most influence over this future marketplace by sharing their knowledge about which factors are most highly correlated with sustainable supply. This visibility would create a different incentive for manufacturing sites to ensure their performance on those key factors is positive and sustainable. The use of the FDA QMM assessments and models will remain important in creating a roadmap for how a firm should build a quality system or how to improve the system they already have, but creating a single FDA gold standard QMM model may no longer be necessary. The FDA can play a key role in educating the marketplace and the industry about how a focus on QMM will lead to a more sustainable supply for patients.

In general, the challenges faced by manufacturing sites in maintaining continuity of supply are not unknown or surprising but result from risk-based decisions made when faced with balancing lack of resources, low-profit margins, and uncertainty of demands against costs of production, human resources, and capital investments. Participation in an FDA sponsored QMM program is certain to add to the burden side of this equation regarding resources and time required, but without much certainty of a positive impact on profits, sales, or business returns. Participation may be a challenging balance for smaller, generic firms to overcome, which, unfortunately, are precisely the sites most at risk of drug shortages in the first place.

Another challenge in translating quality maturity assessment into commercial decision-making information is the complexity of supply chains. A single site level QMM assessment will not indicate overall product supply reliability or be useful to buyers. PDA recommends that the FDA consider whether to assign a QMM assessment that is site specific or for an overall company. Culture can vary from site to site within a given company. While a company may have a solid Quality program and Quality Management System, each site may have its own implementation of the quality elements. If the FDA assigns the QMM assessment for the overall company, PDA recommends that the QMM assessment be a solid cross section of all the sites. Any company-level ratings or results should be a combination of site results with descriptions of how the overall rating was developed.

Finally, assurance of product availability is primarily a function of the product owner (e.g., applicant/manufacturer) and its business continuity planning. Business continuity assessment must include the entire network in the supply chain and often depends on risk-based approaches such as multiple manufacturing sites, multiple suppliers, inventory build at various steps, and investment in product/process improvements. The owner must weigh the potential demand, the impact of other generic or me-too manufacturers for the same product, the impact of better therapies, new regulatory requirements/restrictions against the investment energy, cost, and likelihood of a return. These decisions cannot be taken at the site level and often have a high degree of uncertainty. Further, buyers do not buy from sites; they buy from an owner/manufacturer. It is important to note that for business continuity planning, firms will choose to invest limited resources (human and financial) in products with higher value and more certain long-term demand; therefore, the QMM assessment must consider any product reliability component in this situation.