U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

An Office of Pharmaceutical Quality (OPQ) White Paper

# Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals


## Abstract

CDER is taking another step towards realizing the vision for pharmaceutical quality in the 21st century: a maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight. Research conducted by trade associations, academics, and regulators has demonstrated that Quality Management Maturity is essential to achieving this vision. To increase transparency and incentivize investment in pharmaceutical manufacturing, OPQ is developing a framework to objectively rate the Quality Management Maturity of pharmaceutical manufacturing sites.

## I. Current State: Product Quality is High, Supply Chain Resilience is Low, Drug Shortages Persist

In order for a drug to be approved or licensed by the FDA, a team of physicians, statisticians, chemists, pharmacologists, and other experts must deem it safe, effective, and of sufficient quality. The quality assessment of any drug marketing or licensing application includes assessment of the drug substance and drug product, as well as the proposed manufacturing process, facilities, and control strategy. Pharmaceutical quality is achieved by assuring every dose of a drug on the market is safe, effective, and free of contamination and defects. All sites manufacturing a drug must adhere to Current Good Manufacturing Practice (CGMP) requirements, which define the minimum manufacturing standards to legally market drug products in the United States. Compliance with CGMP requirements assures proper design, monitoring, and controls for manufacturing processes and facilities. FDA facility evaluation and surveillance, including facility inspections, provide assurance that sites manufacturing for the U.S. market comply with CGMP. Together, this regulatory oversight provides U.S. patients and consumers confidence in every dose of medicine they receive.

Patients and consumers also deserve confidence in the *availability* of their medicines. Their access should not be impeded by drug shortages or supply disruptions. The 2019 report Drug Shortages: Root Causes and Potential Solutions by the multi-agency Federal Drug Shortages Task Force reported that 62% of drugs that went into shortage between 2013 and 2017 were associated with manufacturing or product quality problems (e.g., substandard manufacturing facilities/processes or quality defects in the finished product) (1). These problems necessitate remediation, which can take time to address, interrupting production and leading to shortage. The Drug Shortages Task Force found that one of the root causes of drug shortages is the fact that the market does not recognize and reward manufacturers for having mature quality management systems.

> Simple adherence to CGMP standards does not indicate, for example, that a firm is investing in improvements or deploying statistical process control to prevent supply disruptions.

The FDA's Center for Drug Evaluation and Research (CDER) has long held a vision for pharmaceutical quality in the 21st century, which has been described as "a maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight" (2-4). Fully realizing this pharmaceutical quality vision requires moving beyond simply meeting minimum CGMP standards and closer to robust quality management systems. Regulations for drugs in 21 CFR 210 and 211 and guidance in ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

describe the minimum CGMP standards. While both 21 CFR 210 and 211 and ICH Q7 call for routine product quality reviews to identify and address potential issues in a manufacturing process, they do not describe managing continual improvement of the process or quality system.

FDA regularly evaluates manufacturing facilities and takes action, if needed, to enforce CGMP regulations. FDA investigators look for deficiencies in meeting CGMP, but these evaluations do not measure how far a site's pharmaceutical quality system (PQS) rises above the minimum requirements. Simple adherence to CGMP standards does not indicate, for example, that a firm is investing in improvements to prevent supply disruptions. The ICH Q10 Pharmaceutical Quality System guidance augments CGMP with the concept of an effective pharmaceutical quality system over the lifecycle of a product (5). ICH Q10 describes activities to manage and continually improve the PQS (the elements), using knowledge management and quality risk management principles (the enablers).

QMM is the state attained by having consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement.

The Drug Shortages Task Force proposed three enduring solutions to the problem of drug shortages; one solution was developing a rating system to incentivize drug manufacturers to invest in achieving Quality Management Maturity (QMM). QMM is the state attained by having consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement. Gauging QMM requires, in part, determining how well and how thoroughly a manufacturer has implemented the concepts of ICH Q10 (Figure 1)[1]. A transparent rating system could inform purchasers about the level of QMM at sites from which they purchase drugs. In the absence of the transparency generated by ratings of QMM, there is risk that price competition and cost minimization will continue to be key market drivers, especially for generic drugs, without direct reward for manufacturers who actively invest to avoid future shortage. Some pharmaceutical firms have been slow to implement robust, mature quality systems and adopt the quantitative measures of quality that have been successful in the automotive and aerospace industries (6).

1 For example, PQS elements include Process Performance and Product Quality Monitoring System (PPPQMS), Corrective Action and Preventive Action (CAPA), Change Management, Management Review, Quality Planning, and Internal Communication. These PQS elements are foundational for reaching a high level of QMM. Other elements may also be critical to achieving and maintaining QMM such as business continuity forecasting, ensuring availability, robust supply chain management, and leadership commitment that incorporates management review and responsibility.

Transparent QMM ratings could empower manufacturers to identify ways to improve the effectiveness of their PQSs, realize regulatory flexibilities described in ICH Q10, and help move the pharmaceutical industry toward the six-sigma quality common in other industries (i.e., no more than 3.4 defects occur per million opportunities) (7).[2]

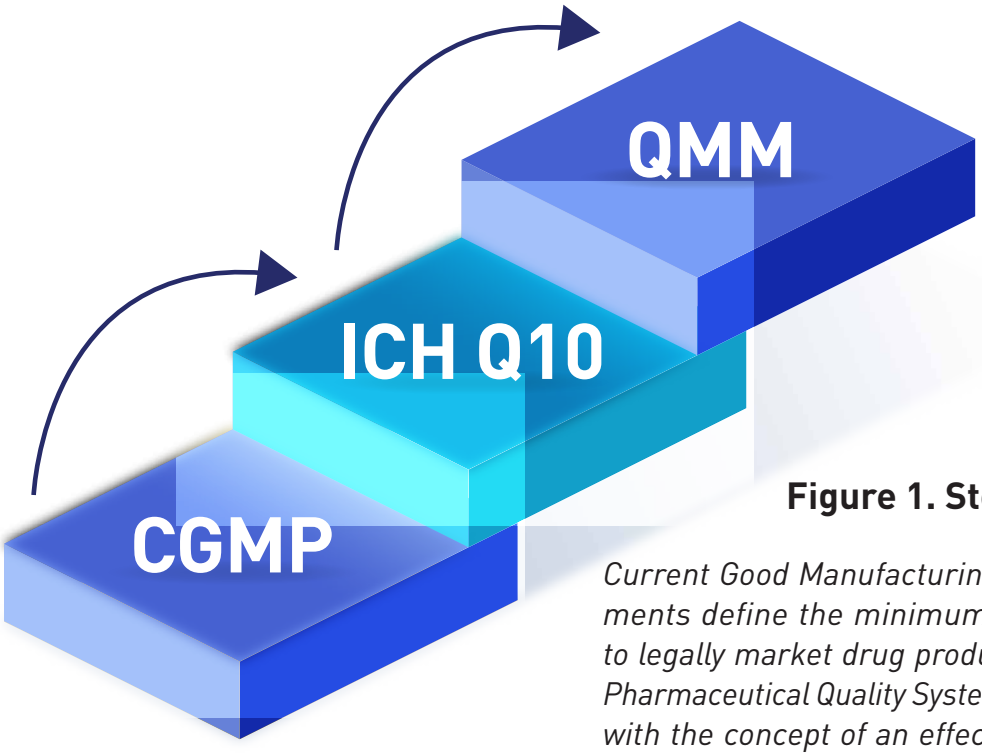



**Figure 1. Steps to QMM**

*Current Good Manufacturing Practice (CGMP) requirements define the minimum manufacturing standards to legally market drug products in the US. The ICH Q10 Pharmaceutical Quality System guidance augments CGMP with the concept of an effective pharmaceutical quality system over the lifecycle of a product. QMM requires, in part, thoroughly implementing the concepts of ICH Q10 to promote continual improvement.*

The need for QMM ratings does not, however, indicate that substandard drug products are on the market. Quality management is part of an array of quality (Figure 2). The FDA assesses product quality in regulatory submissions and monitors the quality of drug products in the U.S. market to provide a high level of confidence in the quality of these products. The FDA assesses formulation, process, and facility quality in applications and monitors and inspects manufacturing facilities to assure risks are controlled. This level of control assures quality in drug product batches released to the U.S. market. Mature quality management uses a performance and patient focus to identify areas of improvement and implement changes accordingly. This type of management gives manufacturers confidence that every batch they make

2 ICH Q10 Annex 1 describes opportunities for flexible science- and risk-based regulatory approaches commensurate with PQS effectiveness. Greater utilization of risk-based approaches with, for example, inspections, regulatory assessments, and post-approval change processes is possible with increasing PQS effectiveness.

will be acceptable to release to the U.S. market. Mature quality management assures that quality product is on the market at entry and over the product's entire lifecycle: quality issues will not keep the product from being available to patients and consumers. Quality management maturity is an expectation in international guidelines (e.g., ICH Q10), but heretofore not actively evaluated by the FDA. An evaluation of QMM is not currently part of the FDA's assessment, inspection, or surveillance processes; the responsibility for QMM falls solely on the manufacturer.

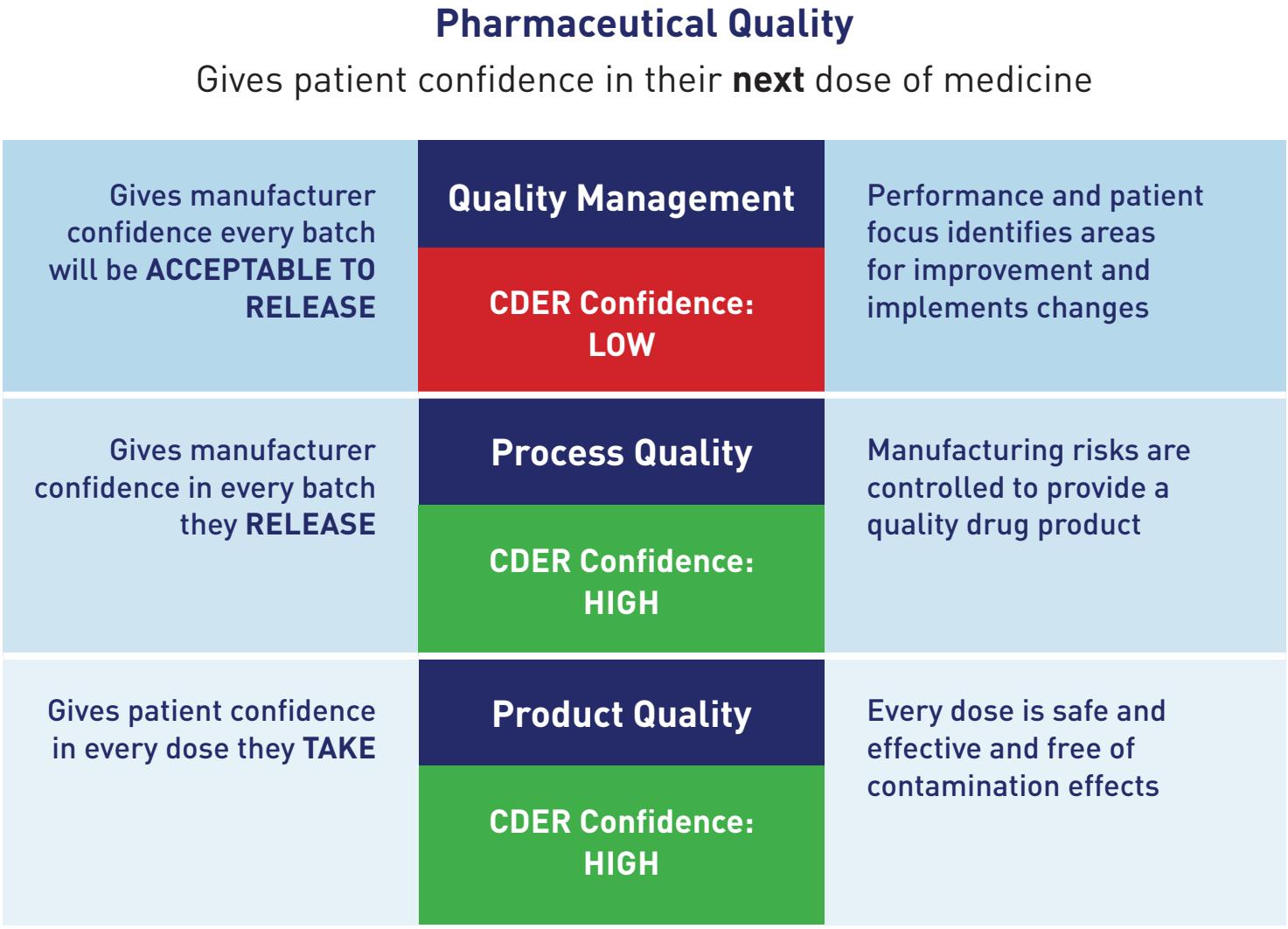



**Figure 2. An Array of Quality**

Drug shortages not only introduce risks to the health of patients and consumers; they stress the healthcare system. A study of 650 physicians by FDA and WebMD in 2018 found that 79% of physicians had patients who experienced difficulty obtaining a medicine due to drug shortage (8). Among cardiologists, dermatologists, and rheumatologists, the percentage was over 85%. There are costs associated with responding to a drug shortage. For example, a pharmacy and physicians facing a shortage may need to seek new ways to access a product, find strategies to work around the shortage, and prepare for an extended impact. One study of over 6,000 U.S. hospitals in 2018 found that 100% of the pharmacies surveyed were affected by a drug shortage in a six-month period and that the majority of those facilities (64%) had managed over 20 shortages in that timespan (9). This study estimated that drug shortages require 8.6 million additional personnel labor hours and over $359 million per year, in labor spending alone, to address at hospitals. Further, 38% of hospitals reported one or more medication errors directly related to drug shortage.

**Mature quality management ensures not only that quality product is on the market now, but that quality issues will not keep a product from being available to patients and consumers in the future.**

Since the drug shortage report's release, many private parties have acknowledged the value of better understanding the behaviors that assure quality and reliability in the pharmaceutical supply chain. Some have begun compiling data and available public information, sometimes in the form of a supply chain rating system and in a fee- or subscription-based model. While a commitment to quality throughout the industry is essential, the FDA is uniquely poised to develop a QMM ratings program. The FDA conducts robust quality surveillance to track facility and inspection data, quality defect reports (e.g., from MedWatch, consumer complaints, recalls, Field Alert Reports and Biological Product Deviation Reports), and drug sampling and testing results. Not all of these data are available to the public. In addition to the need to pay a fee to access private supply chain ratings, some purchasers have indicated their reluctance to use private ratings to drive sourcing decisions without FDA involvement in or backing of those ratings.

Most pharmaceutical purchasers try to collect information on quality in the pharmaceutical supply chain, often with limited success. FDA engagements with purchasers of drugs revealed that many consider some form of quality information in their purchasing decisions, using pragmatic yet limited quality indicators such as location, fill rates,

FDA's notices of objectionable conditions (commonly referred to as Form FDA 483), recalls and warning letter postings, active pharmaceutical ingredient (API) sources, and contract performance history. Purchasers generally have limited visibility into sites' pharmaceutical quality systems and rely on FDA's public information or additional information they can leverage from manufacturers, which they often receive in proportion to the purchasing power of their organization. Regardless, the price to procure and sell generally drives purchasing decisions, which leaves the market without significant and direct reward for those manufacturers investing to avoid future supply disruptions.

## II. Building an FDA Quality Management Maturity Program with Stakeholders

The White House's 100-Day Report on supply chains recommends that the FDA "lead the development of a framework to measure and provide transparency regarding a facility's quality management maturity with engagement from industry, academia, and other stakeholders" (10). CDER has taken a highly collaborative approach to developing a QMM program considering all impacted stakeholders. Development began by building a foundation of science to assure that the fundamental premise of the program was well-reasoned and supported by objective evidence. CDER also extensively engaged with stakeholders potentially impacted by a QMM program to better understand their key concerns and consider them in the development of the program.

### i. Developing a Foundation of Science

Patient and consumer interests are served by risk-based drug shortage prevention and mitigation activities that help to manage supply chain complexities and ensure medicine availability. In response to increasing drug shortages, the FDA issued a Federal Register Notice (FRN) in 2013 to elicit ideas from stakeholders as to how the agency can be more proactive around drug shortages. Quality metrics are used throughout the pharmaceutical industry to monitor quality control systems and processes. In responses to this FRN, it became clear that those in the industry with an early warning system for availability risks use quality metrics. As a result, the FDA recognized a 'blind spot' in regulatory business processes (e.g., inspections, product quality defect reports): nearly all were reactive, focused on detecting negative outcomes. This began a collaborative relationship with industry, academia, and other stakeholders to design and operationalize a quality metrics program focused on being proactive. The FDA's Quality Metrics Initiative was thus born to gather data on certain key metrics to, among other things, incentivize continual improvement and support risk-based scheduling of drug manufacturing facility inspections to decrease inspection frequency for high performers (11).

The use of robust quality metrics programs as the foundation for continual improvement of product and process quality has been validated by extensive research, which has identified clear metrics of performance and cultural excellence (12-14). The effective use of quality metrics is, therefore, one characteristic of robust site QMM. However, as the underlying science has evolved, the conversation has shifted from quality metrics toward a more holistic approach that integrates metrics with other behaviors and attributes of effective PQSs. Metrics remain an important tool to monitor the overall health of a facility and the FDA's Quality Metrics Initiative remains an active and vital aspect of QMM program development.

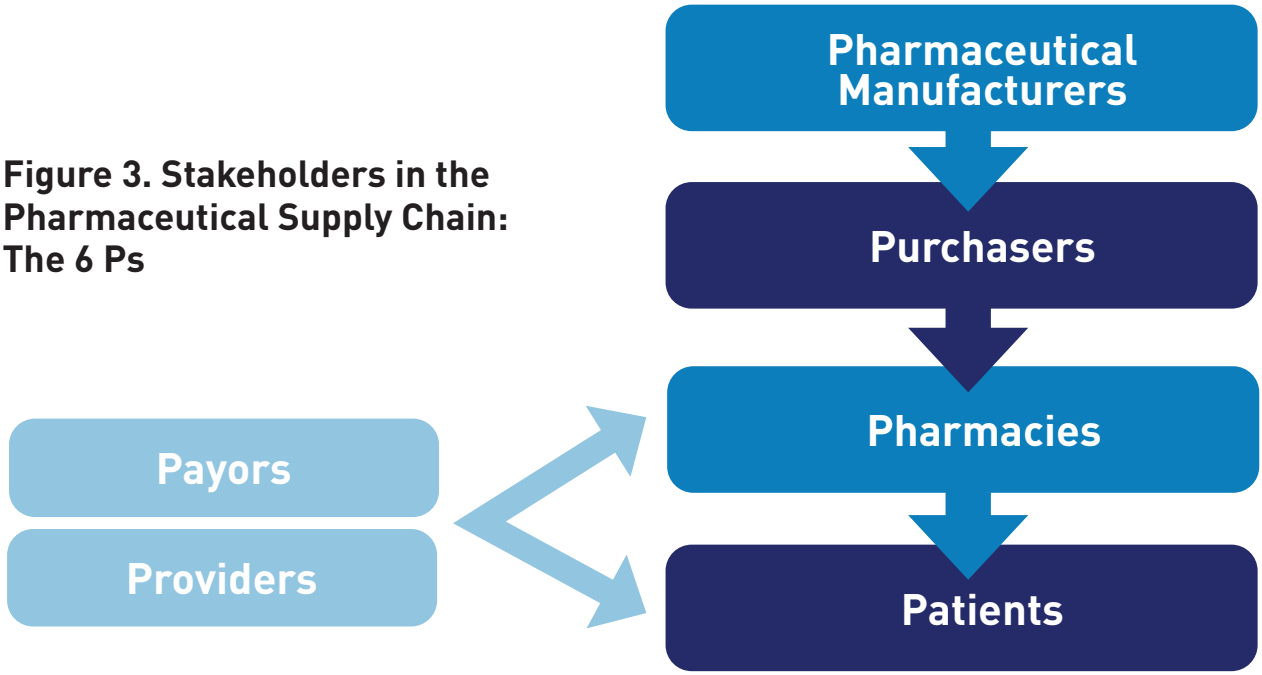
An effective PQS employs quality risk management to manage product availability risks related to hazards in the operations of a pharmaceutical company and its external partners. As explained below, research indicates that mature PQSs lead to substantial efficiency gains related to timeliness, yield, effectiveness, and availability. The integration of manufacturing design, supply partner oversight, and demand forecasting can lead to optimization of inventory levels and improvement in customer service levels (e.g., delivery performance). Therefore, many scientists have hypothesized that sites with more mature PQSs are better able to anticipate and resist supply chain disruptions.

There is now a long history of benchmarking quality culture, operational excellence, and quality management practices in the pharmaceutical industry by the University of St.Gallen (15), the Parenteral Drug Association (PDA) (16), McKinsey & Company (17), and Dun & Bradstreet (18), at times achieved by working in tandem with one another. This breadth of data has allowed researchers to show correlation between quality culture and quality maturity practices and identify the attributes that most strongly differentiate sites based on quality maturity (14). Statistical methodologies have identified potential leading indicators of quality management system performance (19) and the trade organization PDA has even proposed a model for measuring QMM, as they continue to explore the relationship between quality culture, quality metrics, and quality systems (20). CDER-funded research has found, among other things, that firms with a positive workplace culture were less likely to experience drug shortages (unpublished data). There is now mounting evidence to support the hypothesis that sites with more mature quality management practices simply perform better than other sites. CDER funded Dun & Bradstreet to study over 200 global pharmaceutical manufacturing establishments. These researchers found that mature quality management practices positively correlated with performance across locations (unpublished data). A separate analysis by the University of St.Gallen showed that high-performing production sites displayed a higher level of quality system maturity and quality culture/behavior than low-performing sites (21). These findings support the hypothesis that a high degree of QMM has a positive impact across an organization, including on the fundamental ability to deliver supply to patients and consumers.

### ii. Engaging Impacted Stakeholders

The primary stakeholders potentially impacted by a QMM rating program comprise the "6 Ps" of the pharmaceutical supply chain: pharmaceutical manufacturers, purchasers, payors, pharmacies, providers, and patients (Figure 3). Stakeholder engagement has been a critical element in developing a CDER QMM program. In February 2020, CDER sponsored and participated in a workshop held by the Duke-Margolis Center for Health Policy at Duke University on Understanding How the Public Perceives and Values Pharmaceutical Quality. Stakeholders represented at this workshop included patients, healthcare providers, purchasers, pharmacies, and payors. These stakeholders identified three key areas for future work and collaboration across the stakeholder community: (i) assessing perceptions surrounding quality to improve communication, (ii) improving transparency, and (iii) developing quality ratings (22).

**Figure 3. Stakeholders in the Pharmaceutical Supply Chain: The 6 Ps**




Stakeholders at the Duke-Margolis workshop largely agreed that the need to develop and implement quality ratings for the industry is driven by the desire to differentiate products by an attribute other than price and provide a means for purchasers to consider factors other than price. The workshop discussion concluded with the idea that quality ratings may be an ideal topic on which Group Purchasing Organizations (GPOs) and FDA could work together. CDER suggested that, in particular, knowing more about the existing supply chain ratings used by GPOs might help in the development of a rating program. A key stakeholder group, GPOs account for over $100 billion of the drugs purchased in this country in a given year.

Through subsequent FDA discussions with GPOs and other stakeholders, it became clear that purchasers do at times receive limited non-public information about quality management of the supply chain (including data on process capability) from manufacturers through the contracting process. However, these data are more likely to be provided if there is market competition for a product (i.e., multiple sources). Generally, GPOs consider public information (e.g., inspection results that result in a Form FDA 483 citation, warning letters, recalls), location and supply control (e.g., product manufacturing location and API source), and performance history (e.g., fill rates) in rating the supply chain for a given product. GPOs have indicated that they might best use FDA QMM ratings during the bidding process, similarly to how they use homegrown supply chain ratings, and perhaps first in markets with a healthy supply chain history. FDA discussions with pharmaceutical manufacturers have revealed that, in certain contexts, pharmaceutical manufacturers can also be purchasers in the supply chain. For example, a finished drug product manufacturer may purchase API from another manufacturer, or a manufacturer may pay for the services of a contract manufacturing organization. Improved supply chain insight can aid manufacturers in making these types of purchasing decisions. FDA discussions with purchasers and other stakeholders have identified key considerations for developing and implementing a QMM rating program.

## III. Considerations for a QMM Rating System

Operationalizing a QMM rating program for pharmaceutical manufacturers requires a collaborative and transparent partnership between FDA, industry, and other stakeholders. FDA has formed a multidisciplinary, multi-Center working group to facilitate the development of a QMM rating program. This working group is developing a framework to objectively assess and rate the QMM of manufacturing sites using interactive site engagement along with surveillance intelligence. In developing the framework, FDA is considering standardized assessment tools, policy approaches, industry incentives, transparency, and communications. As CDER has started to develop the QMM program, engaged stakeholders have started to identify key challenges to overcome in order to realize a successful program.

### i. Key Challenges for CDER

#### CDER will need to clearly define the scope and meaning of QMM ratings.

Different stakeholders define and use the term “pharmaceutical quality” in different ways. For some, it describes the quality of the manufacturing process and its ability to produce a reliable supply of drugs that is resilient against supply disruptions and shortages. For others, it describes a product that is free of contamination and defects that might affect its safety or efficacy. The FDA will need to clearly communicate the “array of quality” (Figure 2) and draw distinctions between product quality, process quality, and

quality management. It will need to be clear to stakeholders that ratings reflect the QMM at a manufacturing site and not the quality of the product or the process used to make it. Additionally, stakeholders may need to be educated on the meaning or implication of QMM ratings. For example, there is the potential for the misconception that high QMM ratings will be a "guarantee" for a site's products, while a high rating will actually mean that the site has a history of quality management that goes above meeting minimum regulatory thresholds.

### CDER will need to convince purchasers to consider QMM in decision-making.

The current perception among many stakeholders who do not already use some type of supply chain rating in purchasing decisions is that quality of all kinds exists fundamentally if the drug has been approved by FDA. Some do not consider quality management maturity in their decisions. In addition to explaining the array of quality, it may be necessary for CDER to describe the value of using QMM ratings in purchasing decisions to those stakeholders who do not regularly consider quality when making decisions. Though most stakeholders generally support quality maturity ratings, the value may not be as obvious without clarification of program intent and the expected outcomes and benefits.

### CDER will need to clearly separate QMM appraisals from regulatory compliance.

Transparency, engagement, and collaboration are critical to ensuring that pharmaceutical manufacturers understand the QMM program and its implications to pharmaceutical quality and drug manufacturing. QMM assessments and ratings need to be CDER surveillance functions, separate from determining compliance with regulatory standards. Compliance is a prerequisite for a QMM rating. In practice, the ability to assign even the lowest QMM rating implies that a manufacturing site at least complies with minimum regulatory standards.

### CDER will need to rely on purchasers to understand their supply chains.

QMM ratings based on manufacturing sites are of limited value if purchasers do not have insight into the specific facilities manufacturing the drugs or components they intend to purchase, especially as related to API manufacturing. It will be necessary for purchasers to have supply chain information to use QMM site ratings in drug purchasing decisions. The FDA may not be able to disclose specific information about the drug product supply chain and may have to rely on purchasers to procure this information during the bidding or negotiation processes. In conversations with purchasers, FDA found that most purchasers already require supply chain site information as part of their decision-making processes.

### CDER will need the market to reward products from facilities with higher QMM.

Stakeholders mentioned concerns about the purchasing costs associated with higher QMM during engagements. The use of QMM ratings in purchasing decisions should incentivize continual improvement in the long term, but not push manufacturers out of the market and/or markedly raise purchasing costs in the short term (1). Of course, there are long-term cost savings to be realized once higher QMM is achieved. 'Right the first time' drug manufacturing reduces or eliminates: (i) manufacturers' costs associated with out-of-specification batches or product recalls and (ii) healthcare facilities' costs associated with responding to shortage. Additional research may be needed to rule out unintended consequences of QMM ratings, such as market over-consolidation.

### CDER will need to address potential risks of using QMM ratings in decision-making.

Some healthcare professionals indicated that they do not want to be responsible for making comparative quality decisions. Others indicated concerns about liability and risk associated with using QMM ratings in decision-making related to patient care (e.g., issues stemming from providing a drug from a lower-rated facility). Developing QMM ratings based on manufacturing site rather than product removes health care professionals one step from a decision-making process informed by QMM, as they tend to have little or no supply chain site insight, especially as compared to purchasers. Some healthcare professionals also questioned whether drug companies will be allowed to use QMM ratings in marketing their products.

## ii. Key elements of a QMM rating program

Changing the course of pharmaceutical quality by using a QMM rating system is a move toward performance-based regulation of the pharmaceutical industry (7). Most, if not all, key challenges can be overcome by thoughtfully developing and implementing a QMM program. Engagements with stakeholders have helped to identify key elements that will be needed in FDA's QMM rating program.

### Quality culture must be foundational for mature quality management.

Quality culture is an environment in which those who have responsibility for oversight and control over manufacturing taking ownership for quality. Quality culture is demonstrated by organizations in which the objectives drive quality (23). In these organizations, there are not separate business and quality objectives; they are linked together. Although culture must be led from the top, staff at every level an organization must contribute to the commitment to quality. A quality culture is necessary to achieve high levels of QMM.

### A QMM assessment tool must be objective and consistent across manufacturing sites and agnostic to the product or size of operations.

QMM assessments could be carried out by either FDA or a third-party contractor suited to perform such assessments of varied manufacturing sites. Further, the scope and implication of a QMM assessment must be distinct from one determining CGMP compliance (i.e., looking for behaviors and indicators above meeting minimum regulatory requirements). Between on-site QMM assessments, information such as quality metrics could be more routinely submitted to FDA to bolster and support ongoing confidence in the QMM rating of the site.

### A standardized QMM assessment tool must be validated.

QMM ratings must be reliable and consistent between staff conducting the assessments, though a final QMM rating would not be based solely on the results of a site assessment. Other internal or external data may be used to complement the assessment results for a final QMM score, for example, history of drug shortages, past surveillance inspection results, quality metrics, and Field Alert Reports/Biological Product Deviation Reports.

### There must be clear incentives for industry to achieve higher QMM.

There is a cost to supply disruptions and shortages that impacts the entire pharmaceutical supply chain. Potential regulatory and economic incentives for manufacturers related to QMM must be clear. Incentives could include reduced inspection frequency, increased regulatory flexibility in making postapproval changes, and improved supply chain insight. For example, an effective PQS is necessary for firms desiring to use the tools described in ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. Further, purchasers must be willing to consider QMM ratings in their purchasing decisions and, perhaps, pay slightly more for products or components with more robust supply chains. As healthcare professionals, pharmacies, and patients experience the most severe consequences from drug shortages, these stakeholders may need to advocate for the use of QMM ratings in decision-making. For example, without their advocacy there is a risk that purchasers may use QMM ratings to purchase drugs from lower-rated sites for lower prices to realize short-term cost savings. Longer-term thinking is required. More robust and reliable supply chains are outcomes that benefit everyone from pharmaceutical manufacturers to patients in the long term.

### Transparency is critical in establishing a QMM rating system.

Understanding the intentions of the program, along with the ultimate impact on drug shortages and patient outcomes is paramount in convincing pharmaceutical manufacturers to embrace a QMM rating system. Public awareness of a manufacturer's QMM could lead to uncertainty if the meaning of the rating is not clearly defined. It must be very clear that all drugs sold in the U.S. are of adequate quality and considered safe and effective when

taken as directed. A universal understanding of what a QMM rating system means will be for the benefit of all stakeholders. Broader communication to the public will be needed to promote the importance of quality and maintain public trust in their medications.

## III. QMM: A Necessary Step Toward 21st Century Pharmaceutical Quality

FDA is committed to ensuring that high-quality pharmaceuticals are available for patients and consumers, and that the U.S. public has confidence in each dose of medicine. A QMM rating system will foster a more robust drug supply chain and greater commitment to quality in pharmaceutical manufacturing. A QMM rating program that overcomes key challenges and includes key elements will provide benefits for all stakeholders (Table 1) as well as the FDA. Minimally, purchasers and payors will get more insight into the supply chain of the drugs they buy or reimburse, pharmaceutical companies will get more insight into the robustness of their supply chains, and patients, pharmacies, and healthcare professionals get improved clinical care via medicine less at risk of quality-driven shortage.

The FDA will benefit from QMM ratings by being more informed about the quality management practices at sites, allowing for better resource allocation decisions (e.g., inspection timing and frequency) and regulatory flexibility (e.g., related to postapproval changes). This is a move away from focusing solely on negative outcomes and one that will move the FDA closer to performance-based regulation. Perhaps most immediately, QMM ratings will ease the process of regulating postapproval changes. The ICH Q12 guideline provides a framework to facilitate postapproval changes in a more predictable and efficient manner, increasing transparency between industry and regulatory authorities, and supporting innovation and continual improvement. In addition to compliance with CGMP requirements, an effective PQS is necessary for firms desiring to use the tools described in ICH Q12 (24). As noted in the FDA's guidance, while the FDA will not require an inspection before an applicant can make use of ICH Q12 principles, the determination of PQS capability will consider, among other things, conformance with ICH Q10, especially regarding change management practices. Clearly, a robust QMM program will enable CDER to more effectively implement ICH Q12.

In addition to complying with CGMP requirements, an effective PQS is necessary for firms desiring to use the tools in ICH Q12.

FDA has conducted two pilot programs with pharmaceutical manufacturers to inform the criteria used to objectively measure a manufacturing site's QMM. One pilot is focused on domestic manufacturers of finished dosage form products, and the other on foreign manufacturers of APIs. Feedback from the participants in the pilot programs is now helping determine best practices for conducting the assessments, the assessment tool, and associated logistics. Minimizing the burden on manufacturing sites during QMM evaluations is an important consideration in the development of a QMM program.

**Table 1. Benefits for Stakeholders: The 6 Ps**

| Stakeholder | Benefits |
|---|---|
| Pharmaceutical Manufacturers | ✓ Positive and proactive performance acknowledged<br>✓ "Good actors" rewarded |
| Purchasers[3] | ✓ Improved supply chain transparency for decision-making<br>✓ Quality ratings backed by FDA insight and non-public data |
| Pharmacies | ✓ Improved supply chain transparency<br>✓ Less risk of failing to meet demand and medication error |
| Payors | ✓ Improved supply chain transparency for decision-making<br>✓ Less need to respond to drug shortage |
| Providers | ✓ Less risk of drug shortage impacting their patients<br>✓ More confidence in the supply of drugs they prescribe |
| Patients | ✓ Less risk of drug shortage impacting their care<br>✓ More confidence in drug availability |

QMM ratings are a part of an evolution toward performance-based regulatory practice and, as such, they may raise concerns from some. Public transparency is often a necessary driver for industry improvement. Pharmaceutical executives, for example, may not like the fact that a poor QMM rating could affect their stock price. However, public knowledge of facility issues and product recalls already has severe negative consequences to stock price (25).

3 In certain contexts, pharmaceutical manufacturers can also be purchasers in the supply chain. For example, a finished drug product manufacturer may purchase API from another manufacturer, or a manufacturer may pay for the services of a contract manufacturing organization.

In fact, QMM ratings could provide so-called 'good actors' in the industry with less share price volatility. Stakeholders in other industries initially protested the use of transparency and metrics, but now there is general acceptance and recognition of their role in driving quality (e.g., Medicare quality ratings, state reports on cardiac surgery outcomes,and the Physician Payments Sunshine Act) (22). CDER will continue to engage stakeholders during and after the development of the QMM rating program. For example, CDER hopes to further engage with stakeholders by conducting a public workshop to receive feedback on the development of a QMM program, as well as hold an advisory committee meeting in 2022.

The long-term effects of an FDA QMM program could be far-reaching: transparency in the market could provide top-rated manufacturers in the U.S., both large and small, with a competitive advantage, potentially enabling them to grow market share and increase their workforce. Manufacturers with higher QMM focus on continual improvement and are therefore more likely to embrace advanced manufacturing technologies which can improve the capability and robustness of the industry and lead to an expansion of domestic pharmaceutical manufacturing. The potential benefits for stakeholders are clear: manufacturers with higher QMM get recognition in the market; purchasers and payors get more insight and confidence into the supply chain of the drugs or components they buy or reimburse; and patients, pharmacies, and healthcare professionals get medicine less at risk of shortage. Everyone will have more confidence in the next dose of medicine.

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