

Addressing Drug Shortages Through Quality Management Maturity and Supply Chain Reliability Programs

AUTHORS

Stephen Colvill
Thomas Roades
Gerrit Hamre
Marianne Hamilton Lopez
Mark McClellan

SUMMARY

Quality Management Maturity

- In the short term, the U.S. Food and Drug Administration (FDA) should advance the [Quality Management Maturity \(QMM\)](#) program, but with a narrowed scope initially focused on a specific list of vulnerable, essential, multisource generic drugs and the establishments that produce these drugs. An initially narrowed scope would:
 - Encourage immediate focus on preventing the most likely and impactful shortages, with the potential to expand to other drug categories and priorities in the long term, and
 - Reduce administrative cost and burden
- QMM may be more effective if it remains a voluntary program rather than a mandatory program
- Until dedicated funding for QMM is appropriated as recommended below, FDA should continue to use available resources to progress QMM program development and implementation as much as possible

Drug Supply Chain Reliability

- A separate, but closely related, product-level Drug Supply Chain Reliability (DSCR) Program should be established and led by an independent third party. As described below, establishment-level QMM evaluations should be the primary input that plugs into this product-level DSCR program. A DSCR program should:
 - **Be set up now as a pilot program** with oversight from the [U.S. Health and Human Services \(HHS\) Supply Chain Resilience and Shortage Coordinator](#) and other federal agencies, to be followed with Congressional authorizations and funding later
 - **Incorporate crucial drug shortage prevention factors that fall outside of “quality management maturity” practices**, such as backup raw material suppliers, manufacturing flexibilities and redundancies, inventory buffers, domestic and nearshore manufacturing capabilities, and risk management plans
 - **Enable product-specific assessments** that are more impactful for preventing drug shortages and more useful for drug purchasers
 - **Help reduce potential misconceptions around QMM and product quality**, such as the misconception that QMM evaluates whether a drug is safe and effective
 - **Be tied to financial incentives**, such as innovative Center for Medicare & Medicaid Services (CMS) payment programs, tax incentives, price supports, federal grants and loans, and other incentives
- Independent third-party leadership of the DSCR Program can:
 - Increase flexibility and market responsiveness, including speedy program pilots, testing, and adjustments
 - Increase private-sector engagement from purchasers, payers, manufacturers, and others and decrease administrative burden and cost to the government
 - Be set up as a [Federally Funded Research and Development Center \(FFRDC\)](#) with oversight from the HHS Supply Chain Resilience and Shortage Coordinator and other federal agencies. Other relevant models that could be drawn from include the [US Pharmacopeia](#), the [Joint Commission](#), the [National Institute for Innovation in Manufacturing Biopharmaceuticals \(NIIMBL\)](#), [IQVIA](#), and others. In many cases, the involvement of independent third parties has significantly increased voluntary transparency and data sharing in sensitive areas

Recommended Congressional Actions to Address Drug Shortages:

- Congress should authorize and appropriate dedicated funding for QMM.
- Building on QMM, Congress should direct the development and piloting of a product-level Drug Supply Chain Reliability (DSCR) Program, led by an independent third party with oversight from the HHS Supply Chain Resilience and Shortage Coordinator and other federal agencies as described in this issue brief.
 - Establishment-level QMM evaluations should be the primary input that plugs into this product-level DSCR program.
 - As QMM would be the primary input into the DSCR Program, additional funding needs outside of QMM funding could be relatively minor.

INTRODUCTION

A persistent drug shortage crisis in the United States is associated with [higher mortality rates](#), [medication errors](#), [delays in life-saving cancer treatment](#) and other critical medical procedures, as well as [significant financial costs to the healthcare system](#).

The leading cause of drug shortages is low levels of quality management maturity in manufacturing facilities

The leading cause of drug shortages is low levels of quality management maturity in manufacturing facilities (see [Appendix A](#) for definitions of product quality, quality management maturity, and supply chain reliability). Drug payment policies and practices and limited transparency into manufacturers' supply chains means purchasers choose manufacturers largely based on lowest price, which creates adverse market incentives for manufacturers to keep costs down even at the expense of needed investments in supply chain reliability. The Duke-Margolis white papers "[Advancing Federal Coordination to Address Drug Shortages](#)" and "[Supporting Resilient Drug Supply Chains in the United States](#)" both describe these issues in greater detail.

In 2019, the [FDA Drug Shortages Task Force](#) Report noted that "currently, purchasers have only limited information that can be used to assess the state of quality management of any specific facility. . . The lack of information does not enable the market to reward drug manufacturers" for investments in reliability.¹ This need to more effectively and proactively identify reliable manufacturers in an effort to prevent drug shortages has been discussed since at least 2013, when the FDA first issued a [request for public comments on a quality metrics program](#). To solve for this need, the 2019 Task Force recommended creating a rating system that assesses the quality management maturity of manufacturing establishments that can inform purchasing and contracting decisions made by drug purchasers, such as group purchasing organizations (GPOs), pharmacy benefit managers (PBMs), wholesalers/distributors, and health care institutions/providers.²

These recommendations led to the rollout of [two FDA QMM pilot programs](#) that were [completed in 2022](#), ultimately followed by an [FDA request for comment on the QMM program](#) in 2023. This issue brief provides recommendations pursuant to that request for comment.

Implementation and Industry Adoption of QMM and Drug Supply Chain Reliability Assessments are Essential to Solving the Drug Shortage Crisis

Most generic drugs are supplied by multiple manufacturers. Although all manufacturers of a given drug that supply the U.S. market are FDA-approved and are required to meet the same standards for quality manufacturing, that does not mean that every manufacturer offers the same value to their customers (i.e., drug purchasers) or to patients. In other words, manufacturers are "differentiated,"³ but this differentiation between manufacturers currently is not easily identifiable or appropriately valued by

purchasers and payers. For example, one manufacturer may have taken many costly steps to ensure a reliable supply chain, including--but not limited to--the use of modernized production processes and equipment, a strong commitment to quality culture, redundancy and risk management plans, and safety stock inventory levels. Another manufacturer of the same generic drug may have taken none of these steps and may be able to offer a lower price as a result.

¹ Along with helping to address drug shortages for vulnerable, essential, multisource generic products, QMM also can progress other industry-wide initiatives areas as described below. However, the impetus for creating QMM was to address drug shortages, and this issue brief focuses on how QMM's initial and primary focus should be on addressing drug shortages of vulnerable, essential, multisource generic drugs.

² Duke-Margolis white paper "Advancing Federal Coordination to Prevent Drug Shortages" Appendix B contains definitions of different types of drug purchasers.

³ Porter, Michael E. "Competitive Strategy: Techniques for Analyzing Industries and Competitors." 1980.

When drug purchasers choose suppliers, the purchasers generally have little dependable information readily available to them regarding these supply chain reliability investments. Purchasers also have not invested enough on their own into developing resources needed to identify potential risks in their supply chains. Hospital GPOs have taken some steps to identify and reward more reliable manufacturers, such as implementing committed contracting programs in recent years; however, [most hospitals do not participate in such programs or only purchase a small amount of volume through them](#).

Low participation levels in these programs underscore the assertion that differentiation among generic drug manufacturers is currently not easily identifiable or appropriately valued. QMM and a Drug Supply Chain Reliability Program can enable differentiation between various suppliers of the same generic drug, thus helping to identify and appropriately value supply chain reliability, not just lowest cost. Drug purchasers, CMS, private payers, Congress, and others should then utilize the resulting differentiation between manufacturers to create incentives that encourage the use of products with more reliable supply chains. Until such differentiation between generic suppliers is enabled and coupled with appropriate incentives, the drug shortage crisis is likely to continue to worsen.

Along with helping to address drug shortages for vulnerable, essential, multisource generic products, QMM also can advance other areas, such as promoting continuous improvement, creating regulatory and manufacturing efficiencies, and increasing adoption of advanced manufacturing technologies industry-wide. For example, enabling a streamlined post-approval change process for manufacturing establishments that display high levels of quality management maturity may be appropriate in certain circumstances. However, the impetus for creating QMM was to address drug shortages, and this issue brief focuses on how QMM's initial and primary focus should be on addressing drug shortages of vulnerable, essential, multisource generic drugs.

The First Step: Advancing the QMM Program

FDA should advance the QMM program, initially focused on a specific list of vulnerable, essential, multisource generic drugs and the establishments that produce these drugs.

Quality Management Maturity

- In the short term, FDA should advance the QMM program, but with a narrowed scope initially focused on a specific list of vulnerable, essential, multisource generic drugs and the establishments that produce these drugs. An initially narrowed scope would:
 - Encourage immediate focus on preventing the most likely and impactful shortages, with potential to expand to other drug categories and priorities in the long term, and
 - Reduce administrative cost and burden
- QMM may be more effective if it remains a voluntary program rather than a mandatory program

- Until dedicated funding for QMM is appropriated as recommended below, FDA should continue to use available resources to progress QMM program development and implementation as much as possible

Currently, the QMM program is designed to be open to participation from all facilities that manufacture CDER-regulated products. A very large number of sites ([approximately 10,000 sites](#)) are registered with FDA to “manufacture, prepare, propagate, compound or process drugs that are distributed in the U.S. or offered for import to the U.S.,” though not all sites are actively producing CDER-regulated products. Given the QMM program’s primary intended purpose of preventing drug shortages, QMM should begin by prioritizing assessments for a narrower list of drugs (and for the establishments that produce them).

Coordination of this list of drugs with other government entities, for example CMS as it designs payment reforms aimed at increasing generic drug supply reliability, is essential. As previously proposed in our Duke-Margolis white paper [“Advancing Federal Coordination to Address](#)

[Drug Shortages](#),” a cross-cutting federal coordinating entity such as the recently announced [HHS Supply Chain Resilience and Shortage Coordinator](#) should [lead the development of such fit-for-purpose drug lists](#). As a starting point, the QMM program could narrow to injectable formulations of drugs on the [Downselected Essential Medicines Needed for Acute Patient Care](#) list developed by the Advanced Regenerative Manufacturing Institute, with funding from the Administration for Strategic Preparedness and Response (ASPR), but also should note that many very critical drugs, such as those used in life-saving cancer treatment and for chronic conditions, are not currently included on that list and potentially should be added. The list of drugs could be narrowed further to molecules that are highly vulnerable, according to a metric such as [USP Vulnerability Scores](#). However, getting the program started is more important than optimizing to a perfect list, as the list can and should be adjusted on an ongoing basis. Initially narrowing to a targeted list of vulnerable, essential multisource generic drugs can significantly reduce administrative burden and costs both for FDA and manufacturers.

In addition, QMM may be more effective as a voluntary program than a mandatory program. Manufacturers are likely to participate in QMM if that participation gives them an advantage over their competitors. The level of

voluntary participation from manufacturers in QMM will make apparent whether insights generated from the program are useful and whether adequate incentives from payers and purchasers are being put in place to reward manufacturers that perform well in QMM assessments. Slow initial program uptake in a voluntary model could provide a helpful signal as to whether adjustments to the program and/or adjustments to corresponding incentives are needed. On the other hand, if QMM is made mandatory, it may be more difficult to determine the effectiveness of the program. A mandatory program could be more likely to add regulatory burden and costs to manufacturers without a corresponding benefit in terms of reliable supply.

Finally, as in the pilot stages of QMM, it may be most efficient for third-party entities contracted by FDA to carry out establishment inspections and assessments and generate QMM ratings—though FDA could still lead development of the QMM framework and protocols for assessors. This approach, along with the other recommendations included in this section, could allow QMM implementation to proceed swiftly while still achieving the initial aims of the program.

The Next Step: Developing a Drug Supply Chain Reliability Program, with QMM as a Primary Input

Drug Supply Chain Reliability

- A separate, but closely related, DSCR program should be established and led by an independent third party. As described below, establishment-level QMM evaluations should be the primary input that plugs into this product-level DSCR program. A DSCR program should:
 - **Be set up now as a pilot program** with oversight from the HHS Supply Chain Resilience and Shortage Coordinator and other federal agencies, to be followed with Congressional authorizations and funding later
 - **Incorporate crucial drug shortage prevention factors that fall outside of “quality management maturity” practices**, such as backup raw material suppliers, manufacturing flexibilities and redundancies, inventory buffers, domestic and nearshore manufacturing capabilities, and risk management plans
- **Enable product-specific assessments** that are more impactful for preventing drug shortages and more useful for drug purchasers
- **Help to reduce potential misconceptions around QMM and product quality**, such as the misconception that QMM evaluates whether a drug is safe and effective
- **Be tied to financial incentives**, such as innovative CMS payment programs, tax incentives, price supports, federal grants and loans, and other incentives
- Independent third-party leadership of the DSCR Program can:
 - Increase flexibility and market responsiveness, including speedy program pilots, testing, and adjustments
 - Increase private sector engagement from purchasers, payers, manufacturers, and others and decrease administrative burden and cost to the government

- Be set up as a [Federally Funded Research and Development Center \(FFRDC\)](#), with oversight from the HHS Supply Chain Resilience and Shortage Coordinator and other federal agencies. Other relevant models that could be drawn from include the [US Pharmacopeia](#), the [Joint Commission](#), [NIIMBL](#), [IQVIA](#), and others. In many

cases, the involvement of independent third-parties has significantly increased voluntary transparency and data sharing in sensitive areas

Getting Started on a DSCR Pilot

In our recent white paper “Advancing Federal Coordination to Address Drug Shortages”, we outlined a framework for the priorities that a federal coordinating initiative such as the HHS Supply Chain Resilience and Shortage Coordinator could take on, including to “support development and implementation of tools that measure supply chain reliability...for drugs at high risk of shortages”. The proposed DSCR program would fall within that priority, and the HHS Supply Chain Resilience and Shortage Coordinator could act now through administrative action to begin a DSCR pilot program, to be followed by Congressional authorizations and funding later.

Why a Drug Supply Chain Reliability Program is Needed and How It Could Work

A DSCR Program Would Assess Crucial Factors Outside of Quality Management Maturity

A reliable supply chain ensures that patients have access to safe and effective drugs, in adequate quantities, when they are needed. [Quality Management Maturity assessments involve evaluating how effectively establishments monitor and manage quality and quality systems](#) (see more in [Appendix A](#) regarding these definitions). Supply chain reliability and quality management maturity are two related but distinct concepts.

However, many drug shortages driven by low levels of quality management maturity can be and are avoided through reliable supply chain practices such as backup raw material suppliers, manufacturing flexibilities and redundancies, inventory buffers, and risk management plans.

A reliable supply chain ensures that patients have access to safe and effective drugs, in adequate quantities, when they are needed

The root cause of most drug shortages is low levels of quality management maturity at manufacturing facilities, for example, a manufacturer may need to temporarily shut down and remediate a manufacturing line if a sterility issue is detected. However, many drug shortages driven by low levels of quality management maturity can be and are avoided through reliable supply chain practices such as backup raw material suppliers, manufacturing flexibilities and redundancies, inventory buffers, and risk management plans. More expensive drugs that

generate higher profit margins tend to experience fewer shortages than low-cost generic drugs, not only because manufacturers of higher-margin drugs have more incentive to invest in quality management maturity, but also because those manufacturers invest significantly in supply chain reliability practices that enable continued supply in the event of a manufacturing quality issue. In addition, some drug shortages are caused by breakdowns in supply chain reliability from natural disasters, spikes in demand, and geopolitical risks that are unrelated to quality management maturity practices. Some of these other supply chain risks may increase in severity in the coming years.

As a result, quality management maturity should be characterized as a component of supply chain reliability. A distinct product-level DSCR program, including QMM establishment-level assessments as a primary input, is an essential part of addressing drug shortages.

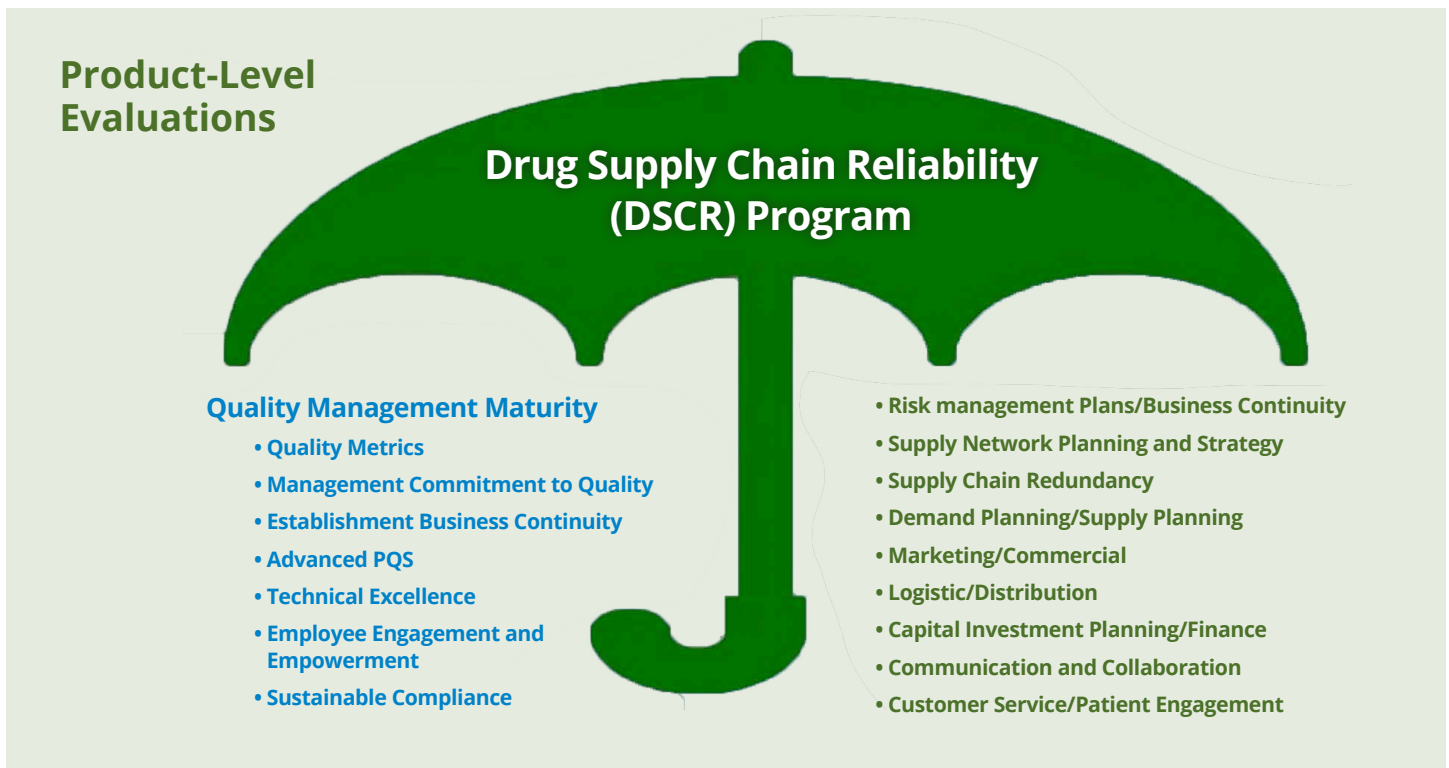
Figure 1 shows the current framework of FDA's Quality Management Maturity program, and **Figure 2** shows our proposed DSCR program framework. The DSCR program is primarily intended to evaluate the performance of manufacturers and their upstream suppliers. Examining

how manufacturers are functionally organized can illustrate further the need to evaluate both quality management maturity and supply chain reliability differently, and also highlight key performance indicators and activities that a Drug Supply Chain Reliability program could evaluate.

FIGURE 1 **Current FDA Quality Management Maturity Framework**



FIGURE 2: **Proposed Drug Supply Chain Reliability Program Framework**



Pharmaceutical manufacturers have corporate quality teams and manufacturing plant teams that are directly responsible for ensuring product quality and quality management maturity. At companies with a strong quality culture, certain other teams (some of which are shown in Figure 3) also share in the responsibility of promoting an environment that emphasizes quality. However, these other teams usually only indirectly contribute to quality, and many of their activities are fully outside

of the quality realm. Some of the activities in Figure 3 are currently included in the Business Continuity practice area of the QMM prototype assessment protocol; however, as the activities below are not quality functions (and as they are generally conducted at the corporate-level and product-level, not the establishment- or facility-level), they are a better fit in our proposed DSCR program than in QMM.

FIGURE 3

Manufacturer Functional Teams	Questions Considered by Functional Team	Example Product-Level KPIs
Supply Network Planning and Strategy	Should we add new capacity? For which products? Are the ingredients of those products U.S.-sourced or otherwise securely sourced? If so, where? Should we qualify backup suppliers? Should we change our manufacturing operating mode such as by removing or adding production shifts?	<ul style="list-style-type: none"> • Historical and Forecasted Demand as % of Total Installed Production Capacity • Number of Backup API Suppliers • Production Operating Mode
Demand and Supply Planning	How many units should we produce and when? How much inventory should we hold?	<ul style="list-style-type: none"> • Fill Rates • Actual Safety Stock Levels • Safety Stock Targets
Marketing and Commercial	How much product demand/customers should we seek given production capacity constraints and other factors?	<ul style="list-style-type: none"> • Historical and Forecasted Demand as % of Total Installed Production Capacity
Logistics and Distribution	How will we distribute our product in the event of a shortage? How quickly can it be distributed? Where should we store inventory?	<ul style="list-style-type: none"> • Time from Order Placement to Shipment • % On-Time Delivery
Finance	Are we making the appropriate level of investment in manufacturing upgrades, innovative technologies, new manufacturing capacity, inventory, or other areas? How much capital should we invest?	<ul style="list-style-type: none"> • Age of Production Equipment • Capital Investment Metrics
Customer Service/ Patient Engagement	How can we effectively communicate with patients and providers in our resilience planning and in case of disruptions?	<ul style="list-style-type: none"> • Customer Service Metrics • Emergency Stock Process Metrics

A DSCR Program Would Enable Product-Specific Assessments

The activities in Figure 3 are conducted by manufacturers very differently for different products, and, as illustrated in Appendix B, supply chain reliability can vary significantly from one product to the next, even when produced by the same manufacturer and at the same establishment. A DSCR program could enable product-specific evaluations that recognize these differences. For example, manufacturer-product combinations could be evaluated separately at the product family, molecule, dosage form, or National

Drug Code level. These evaluations could 1) take as an input QMM establishment ratings for the different supply chain nodes that play a part in manufacturing a particular product as shown in Figure 2 on the left side of the DSCR umbrella and 2) account for product-specific Key Performance Indicators (KPIs) and assessments in Figure 2 on the right side of the DSCR umbrella. Because drug purchasers make contracting and purchasing decisions at the National Drug Code (NDC) level, and because establishment-level ratings may not be significantly indicative of the reliability of a given NDC that a purchaser is considering, purchasers and other

stakeholders have frequently indicated that product-specific ratings would be more useful to them and be more meaningfully embedded into contracting and purchasing decisions. Product-specific ratings also would alleviate challenges that would occur when a product is produced at multiple establishments with differing establishment-level QMM ratings.

A DSCR Program Would Help to Reduce Misconceptions About QMM and Product Quality

While an important concept, quality management maturity is not a widely understood term outside of the field of pharmaceutical manufacturing and pharmaceutical quality. For the layperson, and even many experienced industry professionals, use of the term “quality management” frequently calls to mind the quality of the finished product and whether it is safe and effective. While QMM is not intended to assess finished product quality, and FDA has consistently emphasized this point in messaging, persistent misunderstandings of the QMM program could cause confusion about the quality, safety, and efficacy of the drugs released into the U.S. market. In contrast, the layperson is much more likely to understand that a Drug Supply Chain Reliability Program is intended to assess the ability of manufacturers to consistently supply quality drugs in adequate quantities, when they are needed. Plugging QMM into the DSCR program and emphasizing supply chain reliability assessments thus can help to reduce misunderstandings around QMM and product quality.

A DSCR Program Should Be Tied to Financial Incentives

While additional insights provided by the QMM and DSCR programs are a critical element to address the root causes of chronic drug shortages, these alone will not be sufficient to realign the economic incentives that contribute to drug shortages. Even as information on reliability of manufacturers becomes more readily accessible, purchasing likely will not sufficiently shift toward the high-rated manufacturers. Drug purchasers face many competing priorities and challenging resource constraints and may not choose frequently enough to pay more for more reliable supply chains. An equally important next step beyond the development and implementation of the QMM and DSCR programs will be the development of innovative contracting, payment, and purchasing approaches that incentivize purchasers to pay for more reliable supply.

In the coming months, the Duke-Margolis Drug Supply Chain Resilience and Advanced Manufacturing Consortium will work to advance policy steps that can enable supply

chain reliability assessments and other measurement tools to be factored into innovative contracting, payment, purchasing, and other incentive programs.

Independent Third Party Leadership of the DSCR Program

The DSCR Program should be led by an independent third party with oversight from the HHS Supply Chain Resilience and Shortage Coordinator and other federal agencies. A program situated outside of government could be implemented more quickly and allow for more efficient and agile responses to changes in the market or emerging priorities, as well as speedy program pilots, testing, and adjustments. This positioning also would enable the FDA to focus on its core duties and avoid any perceived conflicts of interest in creating ratings for the same groups they are tasked with regulating.

The independent third party could take the form of a [Federally Funded Research and Development Center \(FFRDC\)](#) and/or a public-private partnership (PPP) model that includes significant private-sector involvement. Pros and cons exist to funding the independent third party with government funds versus a shared investment from the government and the private sector. A government funded model would reduce actual and/or perceived conflicts of interest. A shared investment through a PPP from the government and private sector would reduce government spending needs and also could create more buy-in from drug purchasers, payers, providers, and other stakeholders to ensure that DSCR evaluations provide useful insights and become more embedded into private sector purchasing, contracting, and payment decisions. The PPP approach also would reemphasize the voluntary nature of the program. Group purchasing organizations, providers, manufacturers, and other supply chain stakeholders have shown some willingness to invest funds and other resources in developing shared approaches to prevent drug shortages, as demonstrated through the recent founding of the [End Drug Shortages Alliance](#), the [Healthcare Industry Resilience Collaborative](#), and other initiatives. Whatever approach is taken, the DSCR program should be designed such that it can be incorporated into both government and private sector incentive programs. Examples exist, such as the [Joint Commission](#), of government incentive or payment programs relying on evaluations from independent third parties.

Other relevant models that could be informative include non-profit organizations, such as the [US Pharmacopeia](#) and the Joint Commission, PPPs such as [NIIMBL](#), and for-profit entities such as [IQVIA](#). All of these models have enabled significant sharing of sensitive, confidential information through thoughtfully designed frameworks.

The [International Society for Pharmaceutical Engineering's \(ISPE\) Advancing Pharmaceutical Quality \(APQ\) program](#) and the [Parenteral Drug Association's \(PDA\) Quality Culture program](#), both voluntary, industry-led programs for assessing and communicating levels of quality management maturity, are other models from which to draw relevant insights. The QMM pilots conducted in 2021 and 2022 [used third-party assessors](#), indicating

the feasibility of implementation through a third party; however, we are proposing that the DSCR program be fully led by an independent third party, with oversight from the HHS Supply Chain Resilience and Shortage Coordinator and other federal agencies.

CONCLUSION

As Duke-Margolis has previously recommended, Congress should swiftly authorize and appropriate dedicated funding for QMM. Additionally, QMM should be the primary input that plugs into a Drug Supply Chain Reliability program led by an independent third party. A DSCR pilot program can be setup now through administrative action with oversight from the HHS Supply Chain Resilience and Shortage Coordinator and other federal agencies, to be followed with Congressional authorizations and funding later. When the DSCR program progresses past the initial pilot stage, QMM and DSCR could become more directly connected.

QMM and DSCR programs are necessary elements of a comprehensive approach to address drug shortages. By enabling manufacturers, purchasers, providers, and other stakeholders to identify suppliers making needed investments to reduce the likelihood of drug shortages, the QMM program has great potential to help realign market incentives toward reliability, not merely lowest cost. With the evolutions recommended in this issue brief, implemented in a manner that focuses on drugs most likely to be in shortage and effective and efficient measures of drug supply chain reliability, the program could capture more effectively the factors that contribute to supply chain reliability, build support among and leverage the efficiencies of non-governmental stakeholders, and prioritize the highest-risk categories of products. Collectively, these evolutions would allow the program to be implemented more quickly, more cost-effectively, and with maximum impact in averting drug shortages. These evolutions also address the most common reservations raised by industry stakeholders regarding QMM (Appendix C lists some other common reservations not yet directly discussed in this issue brief).

While additional insights provided by QMM and DSCR programs are a critical element of addressing the root causes of chronic drug shortages, these alone will not be sufficient to realign the economic incentives that contribute to drug shortages. Even as information on reliability of manufacturers becomes more readily accessible, purchasing likely will not sufficiently shift toward the high-rated manufacturers. Drug purchasers face many competing priorities and challenging resource constraints and may not choose frequently enough to pay more for more reliable supply chains. An equally important next step beyond the development and implementation of the QMM and DSCR programs will be the development of innovative contracting, payment, and purchasing approaches that incentivize purchasers to pay for more reliable supply.

The Duke-Margolis Center stands ready to assist with the timely implementation of these programs and next steps and these next steps. In the coming months, the Duke-Margolis Drug Supply Chain Resilience and Advanced Manufacturing Consortium will work to advance policy steps that can enable supply chain reliability assessments and other measurement tools to be factored into innovative contracting, payment, purchasing, and other incentive programs. We look forward to providing further policy recommendations designed to build drug supply chains that provide patients the drugs they need, in adequate quantities, when they are needed.

Appendix A: Definitions and Current State of Product Quality, Quality Management Maturity, and Supply Chain Reliability

This issue brief discusses the concepts of product quality, quality management maturity, and supply chain reliability. Definitions of those terms, along with summaries of the current state, are outlined below.

Product Quality	
Definition	Quality prescription drugs meet quality standards which ensure that the products are safe, effective, and free of contamination and defects. FDA requires that manufacturers of pharmaceuticals marketed in the U.S. comply with Current Good Manufacturing Practice (CGMP) regulations, which are designed to ensure product quality and give patients and providers confidence in the safety and efficacy of the medicines they use. Simple adherence to CGMP quality standards does not indicate that a firm is investing in improvements or deploying statistical process control to prevent supply disruption; that is, it does not assure that CGMPs in supply chains and manufacturing processes will be implemented consistently over time, which in turn leads to the reliable supply of a safe and effective product over time.
Current State	<p>Before a drug is approved or licensed by the FDA, a team of experts provides oversight to clinical trials and deems the drug to be safe, effective, and to meet quality standards.</p> <p>FDA facility evaluation and surveillance, including facility inspections, provide oversight around manufacturing site compliance with CGMP.</p> <p>Every time a manufacturer produces a batch of product and sells it to their customers, the manufacturer attests to the batch's compliance with CGMP.</p> <p>These standards and regulatory oversight help to ensure drug quality.</p>
Potential Next Steps	<p>FDA approval and adherence to CGMP quality standards is sufficient to determine the quality of a drug. Sometimes, manufacturers fail to fully comply with CGMP standards. Resulting impacts include rejecting batches before they are released to the market, Corrective and Preventive Actions (CAPA), negative FDA inspection outcomes, recalls, etc.</p> <p>The standard of quality used by current FDA regulatory initiatives is sufficient to determine the quality of a drug. However, more resources and flexibility in using existing oversight resources to support FDA's current regulatory oversight reform strategy (e.g., modernized data and analytics to prioritize oversight, more unannounced inspections and well-targeted quality testing) could further reduce the rate of noncompliant drugs reaching the US market.</p>

Quality Management Maturity	
Definition	<p>Quality Management Maturity (QMM) is the state attained by having consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement. Quality Management Maturity enables the sustained production of quality drugs over time.</p> <p>Quality management maturity is one of the most important elements of supply chain reliability.</p>
Current State	<p>Too frequently, manufacturers display low levels of Quality Management Maturity. When a manufacturer produces a batch of drug product that does not meet CGMP standards, FDA regulations prohibit the substandard drug product from being released into the market. Manufacturers sometimes do not meet CGMP standards and are unable to release their drug product into the market, resulting in shortages. The "quality issues" cited throughout this issue brief refer to such disruptions in supply. A need exists for greater investment in reliability in production—investments that are separate from CGMP but would be expected to reduce the likelihood of a finished product failing to meet CGMP standards.</p>
	<p>Quality Management Maturity assessments will involve evaluating how effectively establishments monitor and manage quality and quality systems. The five QMM Practices Areas currently included in FDA's QMM prototype assessment rubric are:</p> <ol style="list-style-type: none"> 1. Management Commitment to Quality 2. Business Continuity 3. Advanced Pharmaceutical Quality Systems (PQS) 4. Technical Excellence 5. Employee Engagement and Empowerment

Supply Chain Reliability

Definition	<p>A reliable supply chain ensures that patients have safe and effective drugs, in adequate quantities, when they are needed. A reliable supply chain must have four key components in place (the 4 S's): Staff, Stuff, Space, and Systems. Product Quality and Quality Management Maturity (defined above) are necessary, but not sufficient alone, to achieve a reliable supply chain through the 4 S's. These elements are defined and described in our 2021 white paper, "Supporting Resilient Drug Supply Chains in the United States."</p> <p>Drug shortages result from breakdowns in supply chain reliability. In a reliable supply chain, manufacturers of drugs display a high level of quality management maturity and robustness that enable sustained production and delivery of quality products over time. When a manufacturing quality issue or another disruption occurs, a sufficiently reliable supply chain avoids patient impact through practices such as backup raw material suppliers, manufacturing flexibilities and redundancies, inventory buffers, and risk management plans.</p>
Current State	Too frequently, a lack of supply chain reliability causes patient impact to occur from drug shortages when demand shocks and supply shocks occur, or when adequate steps are not taken to prevent shocks from occurring.

Appendix B: Illustrative Example of Differences in Supply Chain Reliability for Two Products Produced by the Same Manufacturer and at the Same Establishment

Product 2: Low Reliability	Product 2: Low Reliability
High profitability: enables reinvestment in newer, more reliable technologies; production always prioritized for commercial reasons	Addressing Drug Shortages Through Quality Management Maturity and Supply Chain Reliability Programs
Multiple raw material suppliers qualified	Single-source raw material suppliers
Redundant manufacturing capacity, multiple flexible manufacturing lines can run the product	Fully utilized manufacturing line running 24x7, qualified to run on only one line at one manufacturing establishment
Significant days inventory on-hand	Minimal days inventory on-hand
Longer shelf life enables more inventory	Shorter shelf life enables minimal inventory

Appendix C: Other Common Reservations About QMM And How Our Proposed Next Steps Address Them

Reservation 1: QMM ratings will pick winners and losers in the generic drug market.

Response: As described above, identifying and appropriately valuing differences in supply chain reliability of various generic drugs and suppliers, and then putting incentives in place to promote supply chain reliability, is a necessary component of preventing drug shortages. Ratings created by QMM or a DSCR program can help to align market incentives and enable reliable manufacturers to succeed in the market – this is a positive step.

Above, we recommend that such a DSCR rating system should be led by an independent third party, which can increase private sector engagement regarding which manufacturers succeed in the market.

Reservation 2: QMM ratings or a similar program may cause lower-rated manufacturers to exit the market.

Response: According to the IQVIA report “[Drug Shortages in the U.S. 2023](#),” shortages currently are most frequent in multisource generic molecules with a small, concentrated number of suppliers. Many of these molecules previously (for example, shortly after genericization) had a larger number of suppliers, but over time some suppliers have already exited the market. Due to an intense focus by purchasers on lowest price and a lack of supply chain reliability indicators, it is likely that the suppliers that have remained in the market have prioritized offering a low price rather than investing adequately in supply chain reliability practices.

Implementation of QMM or a similar program, when coupled with financial incentives that promote supply chain reliability, has a strong potential to enable highly-rated manufacturers to be successful in the market at marginally higher price points that reflect their value. This approach does not necessitate that lower-rated manufacturers will leave the market; rather, it can enable lower-rated and higher-rated manufacturers to coexist at different price points, unlike the current state of the generic drug market, in which every supplier is generally expected to provide the lowest cost.

While QMM ratings or a similar program could potentially cause some lower-rated manufacturers to exit the market, this may actually have a positive effect on the overall reliability of the drug supply chain by increasing the ability of higher-rated manufacturers to be successful. Lower-rated manufacturers would also have the option to make improvements toward a higher rating, as the program is intended to identify opportunities for continual improvements, regardless of rating.

To reduce barriers to entry for new market entrants and to reduce concerns about lower-rated manufacturers exiting the market, incentive programs could be applied to only a certain portion of purchases in the market.

Reservation 3: Confusion exists around the meaning of “maturity” within “quality management maturity”. Could this be misinterpreted to mean that older facilities are more reliable than newer facilities?

Response: “Maturity” is independent of the age of facility. Newer facilities are often more likely to use more modernized production processes and equipment and thus be more likely to achieve higher states of quality management maturity.

By focusing incentives on a Drug Supply Chain Reliability Program, potential confusion around the term “maturity” would be reduced or eliminated.

Reservation 4: QMM ratings may be subject to bias.

Response: As it does with CGMP inspections, FDA should take steps to reduce bias in QMM evaluations as much as possible. The staff involved with the QMM program are developing a standardized assessment rubric designed to reduce this bias. However, qualitative components are an important aspect of a comprehensive evaluation, and some risk of bias is possible in any qualitative assessment. Focusing on defined key performance indicators (KPIs) can also help to reduce bias.

Reservation 5: Should we ramp up FDA inspection frequency and intensity instead, especially in foreign establishments?

Response: Increasing FDA inspection oversight could be a smart step to provide an incentive for quality manufacturing, but a decision on whether to do this is likely independent of a future direction for QMM. Increasing regulatory oversight further comes with a risk of reducing competition in the market, increasing the burden on quality manufacturers, and causing low-performing manufacturers to exit the market.

Regardless of whether FDA ramps up inspection frequency and intensity, the QMM and DSCR programs should proceed to enable a well-functioning market that differentiates between higher-rated and lower-rated manufacturers and products.

Taking steps such as improving FDA's ability to perform unannounced facility inspections in some foreign countries would likely be beneficial, but this approach is not a standalone solution to drug shortages. Many manufacturing quality issues and aging facilities exist in the U.S., and many of the most severe drug shortages have been triggered by manufacturing quality issues at U.S. sites.

Reservation 6: Providers may face legal liability if using a lower-rated drug.

Response: All manufacturers of a given drug are FDA-approved and are required to meet the same standards for quality manufacturing. Lower QMM and DSCR ratings will not indicate that a drug is less safe or less effective, so providers should not face any legal liability for using a lower-rated drug.

In addition, FDA already distinguishes between different manufacturing sites by providing Official Action Indicated (OAI), Voluntary Action Indicated (VAI), and No Action Indicated (NAI) inspection outcomes, yet no issues of provider liability have surfaced from this practice.

Focusing on a DSCR program will further reduce or eliminate the potential misconception that a product with a lower rating may pose a potential quality or safety risk to patients.

Acknowledgements

The Duke-Margolis [Drug Supply Chain Resilience and Advanced Manufacturing Consortium](#) consists of a group of experts in supply chain, manufacturing, regulatory science, national security, and drug shortages from academia, private industry, governmental agencies, and additional relevant stakeholder groups. The Consortium's mission is to identify effective policy solutions that promote a resilient drug supply chain with advanced manufacturing capabilities and, ultimately, reduce the frequency and severity of drug shortages.

The recommendations and analysis in this white paper represent the thinking of Duke-Margolis researchers, which has been informed by Consortium activities and the expertise of its members. As part of Duke University, Duke-Margolis honors the tradition of academic independence on the part of its faculty, researchers, and scholars. Neither Duke nor the Duke-Margolis Center takes partisan positions, but the individual researchers are free to speak their minds and express their opinions regarding important and pertinent issues. This white paper may not represent the opinions of every Consortium member. This publication is not intended to limit the ability of Consortium members to provide their own comments on behalf of their independent organizations.

Disclosures

Mark B. McClellan, MD, PhD, is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomiQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Arsenal Capital Partners, Blackstone Life Sciences, and MITRE.

Stephen Colvill, MBA, is Executive Director and Co-Founder of RISCs, a non-profit drug supply chain rating and certification organization with a mission to prevent drug shortages. Stephen serves on the board of the End Drug Shortages Alliance and as an advisor for Angels for Change and Medicines360.