Economics and Risks Associated with FDA's QMM Rating Program

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EXECUTIVE SUMMARY[1]

The Food and Drug Administration's Center for Drug Evaluation and Research through the Office of Pharmaceutical Quality in 2021 embarked on an initiative to develop a framework for establishing a pharmaceutical manufacturing site quality rating system, the Quality Management Maturity (QMM) program.[1] One of the recommendations in a report by the Drug Shortage Task Force called for the implementation of such a ratings system that would provide pharmaceutical buyers greater transparency to differentiate the quality management of drug products among manufacturers. Such transparency would incent pharmaceutical manufacturers to establish practices and processes consistent with broader-based risk management frameworks and pharmaceutical quality system (PQS) guidance as described in ICH Q10 and beyond.

This study presents an economic analysis of the effects of a manufacturing quality rating on the pharmaceutical industry. Examination of current market structure conditions including the degree of competitiveness among market participants in negotiating prescription drug product contracts is analyzed along with a machine learning analysis of the duration of drug shortages. Alternative economic models and numerical analysis highlight the existence of information asymmetries preventing pharmaceutical buyers to differentiate between manufacturers for specific drug products. Despite a market characterized by price inelasticity, the analysis suggests that quality ratings should incent manufacturers to invest in quality processes with an aim toward reducing drug shortages. Several use cases from other industries and products where quality ratings or standards have been introduced further indicate that such ratings assessment processes have the potential to elevate the industry's awareness to and focus on quality management maturity.

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OVERVIEW & STUDY MOTIVATION

The Food and Drug Administration's Center for Drug Evaluation and Research through the Office of Pharmaceutical Quality in 2021 embarked on an initiative to develop a framework for establishing a pharmaceutical manufacturing site quality rating system, the Quality Management Maturity (QMM) program.[2] One of the recommendations in a report by the Drug Shortage Task Force called for the implementation of such a ratings system that would provide pharmaceutical buyers greater transparency to differentiate the quality management of drug products among manufacturers.[3] Such transparency would incent pharmaceutical manufacturers to establish practices and processes consistent with broader-based risk management frameworks and pharmaceutical quality system (PQS) guidance as described in ICH Q10.

Today, pharmaceutical manufacturers of products marketed in the United States are required to comply with Current Good Manufacturing Practice (CGMP) standards, which represents a regulatory minimum on quality. CGMP standards promote manufacturing and process quality by ensuring that drug products meet the "safe and effective" criteria set forth by FDA. QMM seeks to elevate quality management among pharmaceutical manufacturers beyond CGMP requirements relating to aspects of manufacturing design, development, and operational processes. As such, quality management takes on a more holistic approach to promoting a process of continuous improvement in managing the drug product life cycle. QMM effectively attempts to measure a company's adoption and implementation of ICH Q10 standards.

Quality management is intended to assess and strengthen processes aimed at improving the customer experience including the quality of products provided. The ideas for quality management have historical roots in work by Deming, for example, who introduced concepts for statistical control in production processes and other quality measurement and management practices.[4] Deming's work has been heralded as revolutionizing Japanese manufacturing following World War II, most notably their automotive industry that had suffered for years with quality and brand reputation issues. Approaches to quality management vary from industry to industry and include standardized approaches

such as ISO 9000/9001 as well as Total Quality Management (TQM), Continuous Quality Improvement (CQI) and Six Sigma practices.[5]

Manufacturing ratings processes exist across many industries as will be reviewed in this study as use cases for comparison with the FDA QMM Program and vary in terms of the purpose of their application, the entity responsible for formulating and disseminating the ratings and the relative adoption of ratings across an industry. Examples of where variations of product manufacturing quality ratings are used today include the automotive and aerospace industries, and even financial services, among others.

One of QMM's expected benefits is to prevent the occurrence of a drug shortage. The Drug Shortage Task Force identified a number of contributing factors to drug shortages including a lack of market and regulatory incentives for manufacturers to implement quality management systems in their processes. The Task Force noted that a general lack of transparency regarding the quality management processes established by pharmaceutical manufacturers, and negligible financial incentives among pharmaceutical purchasers to promote manufacturer quality management programs can lead to drug shortage events due to deficiencies in underlying processes that lie beyond the detection of some manufacturers.

Another contributing factor to drug shortages cited by the Task Force was the economic landscape and market structure under which pharmaceutical manufacturing takes place. This market is characterized by a diverse array of products with varying degrees of profitability, demand and pricing uncertainties, market segmentation and concentration on the demand and supply side as well as regulatory complexities that can at times lead to drug shortages for products due to a highly competitive market where investment in QMM manufacturing processes may not be of first order importance to a manufacturer pursuing a strategy of short-term profit maximization.

The nexus of quality management and market structure as potential factors contributing to drug shortages forms the basis for this study with specific focus on how QMM could provide a mechanism through which financial incentives could factor into prescription pharmaceutical product contracts with manufacturers to enhance manufacturer adoption

of quality management practices consistent with ICH Q10 and beyond. Several questions of interest this study seeks to answer are the following:

1. What are the characteristics of the market structure associated with pharmaceutical manufacturing in terms of demand and supply that need to be considered in developing a manufacturing rating system? Of specific interest is the nature of competition and market power between buyers and sellers of pharmaceutical products, market segmentation, inherent complexities of the pharmaceutical supply chain, and profitability and cost structure that could affect the impact of a quality ratings system on manufacturer adoption of QMM practices. To examine this question, a broad survey of characteristics of buyers and sellers, the market landscape and potential effects on drug shortages is conducted including an empirical analysis leveraging several FDA and financial data sources.

2. What economic model best describes the current state of pharmaceutical product manufacturing where no QMM rating system exists? The study develops a theoretical model of pharmaceutical manufacturing under several different types of markets and tests the economic theory in a numerical analysis of these markets.

3. How would a QMM rating system potentially change buyer and seller (manufacturer) behavior, especially in terms of adoption of QMM principles by manufacturers? The economic models used to answer Question 2 are then examined under a hypothetical scenario where an industry-wide mandatory QMM rating is required.

4. What use cases from other industries could inform how the QMM program might benefit from such experiences? Several industries are selected as use cases for highlighting their use of quality ratings in product development or manufacturing. Industries selected include medical devices, banking, nursing home facilities, automotive, and industrial manufacturing. The review of industry use cases is specifically focused on the following:
   o How ratings are applied
   o The effect of ratings on contract negotiation and pricing
   o The influence on quality ratings on the adoption of quality management principles by suppliers

5. What risks to the market could arise from the implementation of QMM? Of specific interest here are unintended consequences that result from how buyers

use ratings and their associated effects on manufacturers. For example, could implementation of QMM be counterproductive by facilitating manufacturer consolidation of less profitable manufacturers that are unable to invest in quality management? If so, could introducing greater transparency to the market in terms of quality management practices via a rating process segment the market into high and low quality manufacturers that, rather than incent broad adoption of quality management, reduces industry diversification and stifles competition which could result in raising pharmaceutical prices; an outcome clearly contrary with public policy? This is one of the many issues explored in the study.

A SURVEY OF PHARMACEUTICAL MANUFACTURING MARKET STRUCTURE & SUPPLY CHAINS

One of the notable characteristics of the pharmaceutical supply chain is its complexity among a diverse array of market participants.[6] For obvious health and safety reasons, this is a highly regulated industry. Regulation is one of the most influential factors affecting pharmaceutical manufacturing market structure as it affects both the costs associated with bringing drug products to market, minimum quality standards for manufacturing and end products, market segmentation and economics. The success of a manufacturing quality rating depends in part on the willingness and ability for key market participants in the pharmaceutical supply chain to adopt such ratings to affect manufacturer behavior toward practices that improve quality. A review of the major participants affecting demand and supply of pharmaceutical products along with the mechanics of pricing, payment and product flows, market incentives and other important features is reviewed in this section.

DEMAND-SIDE PARTICIPANTS

Consumers of pharmaceutical drug products are effectively the end users in the supply chain and demand for these products typically is enabled via a health plan sponsor such as an employer and a health plan provider. Sponsors can be private or public. Plan sponsors pay premiums to health plans as do consumers for coverage of pharmaceutical products. Delivery of pharmaceutical products in the United States largely come from two channels: retail pharmacies and healthcare providers at hospitals and other healthcare facilities. Central to understanding the touchpoints with manufacturers are a

set of market intermediaries providing a range of services for pharmacies or healthcare organizations. Some of these organizations are so large that by the size of their customer or member networks (pharmacies or healthcare providers) help counterbalance the market power of pharmaceutical suppliers.

For the retail channel, pharmacy benefit managers (PBM) feature prominently as an intermediary between drug suppliers and pharmacies. PBMs provide administrative services for health insurance plans and plan sponsors associated with managing pharmaceutical programs including negotiation of drug pricing with manufacturers which can include performance incentives and rebates. Most consumers today obtain their prescriptions from large retail chain pharmacies such as Walmart, CVS and Walgreens, where market concentration among PBMs is high.[7] In 2020, 79% of all prescription claims managed in 2020 were from three PBMs; CVS Caremark 34%; Express Scripts 24%; and OptumRx (UnitedHealth) 21%.[8]

For the healthcare industry, group purchasing organizations, (GPOs) serve as intermediaries between their members (e.g., hospitals) and manufacturers. Membership in a GPO is voluntary, however, like PBMs, there is a significant concentration among a few GPOs.[9] According to one source, 4 GPOs accounted for approximately 90% of medical supplies in the US.[10] GPOs negotiate contracts with manufacturers including pricing primarily for generic drugs as well as discounts on these products. [11]

SUPPLY-SIDE PARTICIPANTS

New drug development is a long duration, high cost, low payoff probability endeavor that is facilitated by patent protection once a product comes to market in contrast to the generic drug product development cycle. As a result, products are segmented into brand and generic types. Given the protection afforded to brand products, pharmaceutical manufacturers of these products tend to enjoy greater profit margins than generic companies during initial marketing. [12] Pharmaceutical manufacturing is conducted globally, and subject to individual country regulations for manufacturing quality, import and export requirements. Manufacturing occurs in vertically integrated organizations or can be outsourced to contract development and manufacturing organizations (CDMOs). The degree of competition within a particular product varies considerably. Some

products may feature only a single manufacturer; perhaps a specialized or niche type of drug product, a brand manufacturer, or even a product that has declined in profitability leaving a single manufacturer left. This can have significant consequences on market power exerted by suppliers in terms of product pricing and on the risk of a drug shortage. To gain a perspective of the nature of competition within the market, data on the number of applicants for a specific drug product that was reported in the FDA's Orange Book data is presented in Table 1.[13] The data support the point that the degree of competition within a pharmaceutical product varies. The distribution of applicants appears to be somewhat bar-belled; with 40% of drug products having a single applicant and 32% having more than 5. From this view, the pharmaceutical market appears skewed toward a less competitive market; i.e., fewer sellers for many drug products.

Table 1 Number of Drug Product Applicants (FDA Orange Book)

Number of Applicants per Drug Product	Number of Drug Products	Percent of Total
1	720	40
2	179	10
3	140	8
4	98	6
5	76	4
>5	569	32

An alternative view of the nature of competition on the supply-side of the pharmaceutical market emerges when looking at only drug products in shortage over time. Merging data from the FDA Orange Book and Drug Shortage data, Table 2 reveals that a greater share of drug products in shortage are from products with a larger number of applicants. Further examination of these results will be explored in the section analyzing data from drug shortages. The number of buyers and sellers and their degree of market power determines whether a market is competitive or not according to standard economic theory. It should not be surprising that pharmaceutical manufacturing is comprised of both small and large companies with submarkets for individual drug products ranging from competitive to noncompetitive.

Pharmaceutical manufacturing can further be subset between companies that focus on finished dosage form (FDF) products or active pharmaceutical ingredients (APIs) that are used in manufacturing FDFs. This is a critical distinction for the utility of a quality ratings system. A quality rating system applied to both FDF and API manufacturers may have a better chance at affecting overall manufacturing quality and thus reducing drug shortages than assessing quality on just one manufacturing segment. The QMM Program

Table 2 Number of Drugs in Shortage Applicants (Merged Orange Book and Drug Shortage Data)

Number of Applicants per Drug Product	Number of Drug Products	Percent of Total
1	18	13
2	10	7
3	8	6
4	12	9
5	6	4
>5	87	61

Source: Merged data from FDA Orange Book and Drug Shortage Databases

piloted a ratings system for small groups of API and FDF manufacturers. A question remains, however, regarding the extent to which FDF manufacturers would adopt a quality rating to use in vetting API suppliers and its effect on drug shortages. If adoption of QMM ratings by API manufacturers was low among FDF manufacturers, even if adoption of ratings for FDF manufacturers was high, the potential for an API-induced drug shortage could still exist, absent contractual requirements by the purchaser for both the API and FDF rating, limiting the effectiveness of the rating system to alleviate drug shortages in general.

Most pharmaceutical products are sold by manufacturers to wholesale distributors that directly sell these products to dispensing organizations, i.e., pharmacies or healthcare providers. Wholesalers manage pharmaceutical inventories and logistics and delivery associated with bringing product to market. And similar to GPOs and PBMs, there is a high degree of concentration among wholesalers. Three wholesale distributors, AmerisourceBergen, Cardinal Health and McKesson account for 92% of the market.[14]

Profit margins for this activity generally tend to be low (depending on the drug and whether it is a brand or generic) with manufacturers selling to wholesalers near wholesale acquisition cost (WAC) adjusted for any negotiated discounts. The price paid by a pharmacy or healthcare organization is negotiated with the PBM or GPO from that wholesale price.

RETAIL PHARMACY SUPPLY CHAIN NETWORK

A schematic of the retail pharmaceutical supply chain is presented in Figure 1. Key interaction points on the supply side are between API and FDF manufacturers (or CDMOs if products have been outsourced for manufacturing). Potential delays in access to APIs or contamination could pose a downstream shortage for an FDF manufacturer. Consequently, the quality of API manufacturers should be of importance as mentioned earlier to FDF manufacturers should manufacturing quality ratings be leveraged by PBMs in their contract negotiations.

Note that while PBMs negotiate pricing, any discounts or rebates; the physical transfer of drugs products happens between the wholesaler and pharmacy with negotiated payments from the PBMs flowing to the pharmacy. From the standpoint of how a rating system might affect manufacturer behavior, the degree of market power wielded between PBMs and manufacturers is an important driver determining pricing discounts and other concessions including performance guarantees or standards.

HEALTHCARE PHARMACEUTICAL SUPPLY CHAIN NETWORK

The role of the GPO in the healthcare pharmaceutical supply chain is shown in Figure 2. The contact points on the supply- and demand-side are comparable with the retail pharmacy supply chain with some notable differences. The GPO can negotiate with both the manufacturer and the wholesaler as needed with regard to pricing for their healthcare members.[15] And like the retail pharmacy supply chain, the extent of price discounts and concessions depends on the relative market power between demand and supply-side participants. These market dynamics will be explored in greater detail in the section outlining the economics of the supply chain.

Other differences relate to the formularies developed by hospitals that direct prescribers toward higher margin drug products. This provides GPOs with more leverage in negotiating prices than perhaps a PBM. Moreover, there is greater transparency in terms of discounts negotiated by GPOs than PBMs. Typically, a discount negotiated by a GPO would be billed back to the manufacturer by the wholesaler whereas a rebate negotiated between a PBM and manufacturer is not visible to the wholesaler. The visibility of the discount to the wholesaler in a GPO-based contract thus might reduce a manufacturer's incentive to permit substantial discounts in a GPO negotiation.

Figure 1 Representation of the Retail Pharmaceutical Supply Chain
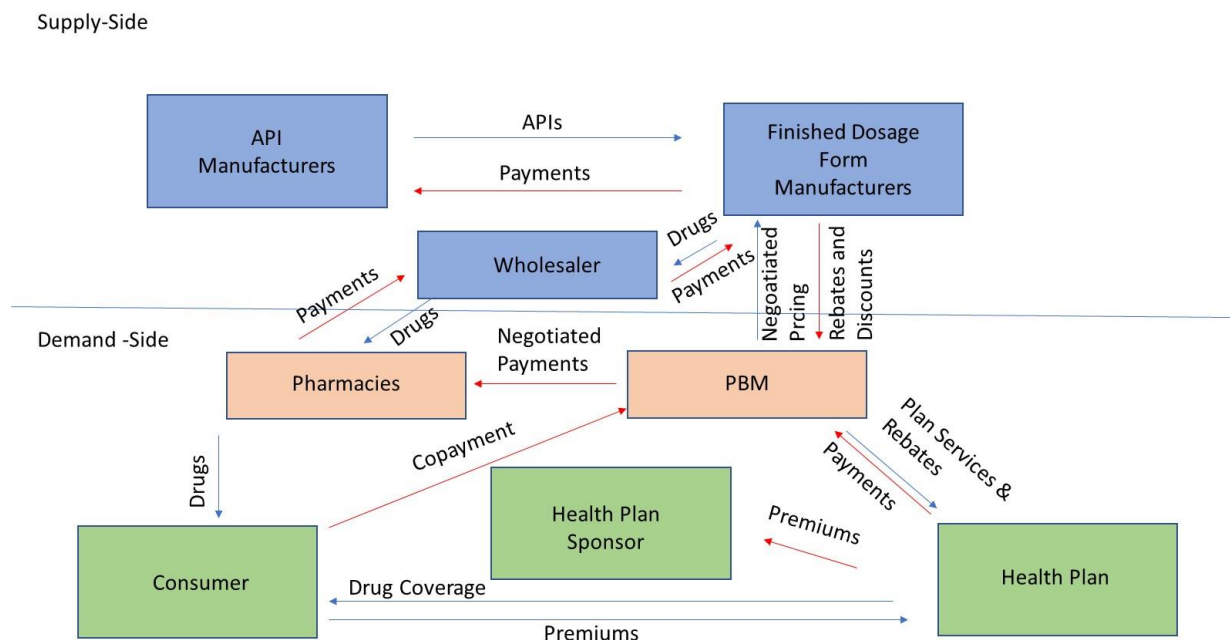
The structure of pharmaceutical contracts and tactics used by buyers of pharmaceutical products is central to how manufacturing quality ratings could incent manufacturers to invest in quality processes and practices. Over time, as purchasing organizations have become more concentrated, their ability to extract favorable concessions in the form of vendor fees or sole source premiums for including their products in purchaser formulary catalogs has grown.[16] Drug buying organizations may extract rebates or discounts from manufacturers which they can in whole or partially pass along to plan sponsors. There has been some discussion among policymakers and industry observers that a safe harbor

carve-out from the Anti-Kickback Statute (42 U.S.C. § 1320a-7b[b]) provided for GPOs and PBMs can promote a concentration of supply for certain drugs in one or a few suppliers. Certain drug products with low net prices tend to be placed on a preferred formulary tier than other products. Rebates can be negotiated with manufacturers, trading volume for a drug product for discounts in product formulary tiering placement as a mechanism for driving volume to a particular product. In cases where a close

Figure 2 Representation of Healthcare Provider Pharmaceutical Supply Chain
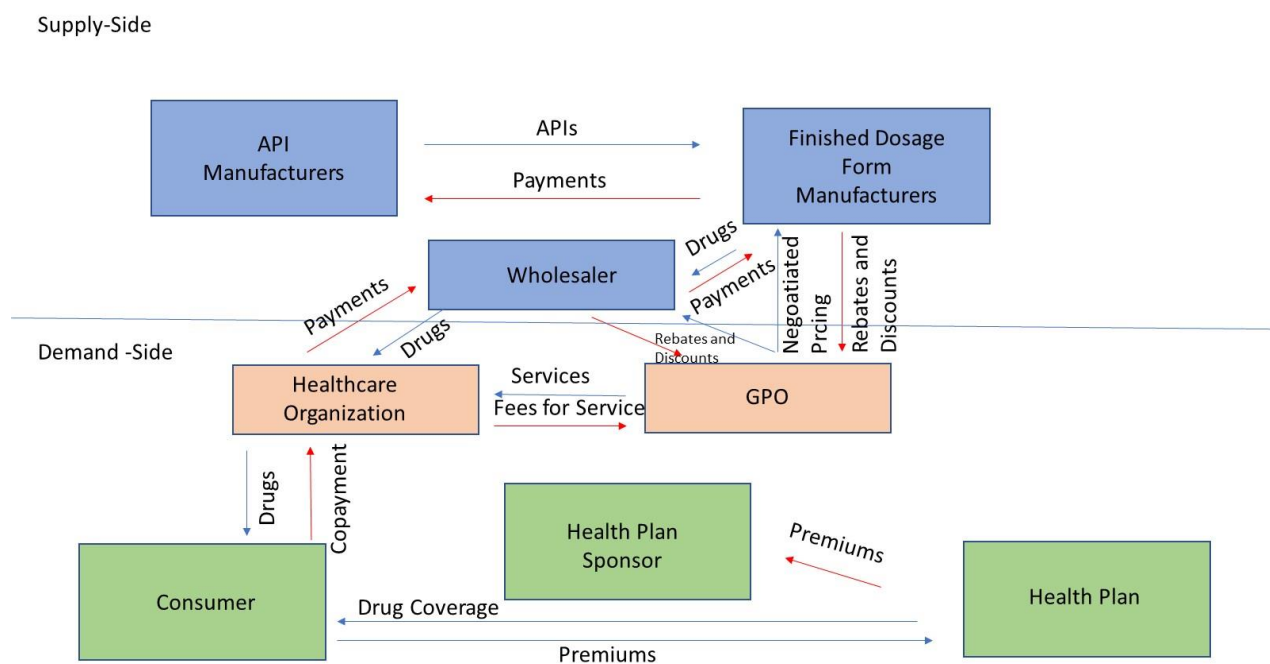
substitute does not exist for a product, the drug buyer loses their market power to extract price discounts. Market power exerted by large buyers can dampen the ability of manufacturers to raise prices which is beneficial to downstream consumers but could also affect the potential for quality manufacturing and drug shortage frequency. An erosion in profit margin can reduce incentives to invest in manufacturing quality, as well as in some cases lead to a lack of supply diversification due to sole source pricing.

The costs associated with drug shortages are sizable. According to a survey conducted by the large GPO Vizient in 2019, it is estimated that the annual costs of a drug shortage to hospitals is $360 million.[17] This includes the time and additional costs associated with

researching suitable drug alternatives. These costs are not directly negotiated in contracts between buyers and sellers. Since there is no industry-wide manufacturing quality rating system in place, the inability to distinguish manufacturers on the basis of quality management maturity implies that drug shortage costs are unable to be priced for in the market. As will be examined in the next section, this lack of product differentiation on the basis of QMM for a specific drug product has implications for manufacturing quality ratings as a mechanism to reflect these costs more directly in pricing and/or via other performance guarantees or standards that could reduce the potential for drug shortages and their costs on dispensing organizations and customers.

ECONOMIC MODELS FOR ASSESSING THE IMPACT OF A MANUFACTURING QUALITY RATING SYSTEM

The purpose of this section of the study is to examine the effect on manufacturer and purchaser behavior, market pricing and product equilibrium conditions with and without a manufacturing quality rating system in place. Given the complexity and diversity of pharmaceutical products, manufacturers and purchasers of these products, relying on a single economic model to describe various pharmaceutical submarkets is insufficient. The degree of competition among pharmaceutical manufacturers and market power they have affects market pricing, output and incentives for manufacturers to invest in quality processes.

In one of the largest drug markets in the US, Medicare reimbursements to healthcare providers of drugs purchased from wholesalers illustrates how market power can influence manufacturer investment decisions. One study, for example, examining the role of federal reimbursement policy on drug shortages found that when Medicare reimbursement policy changed from using Average Wholesale Price (AWP) to Average Sales Price (ASP), it significantly reduced provider reimbursements and indirectly lowered pricing to manufacturers. [18] The model used in the study suggested that manufacturer investment in processes that increase production reliability and quality were a function of expected returns. In turn, the change from AWP to ASP pricing reduced incentives, i.e., financial returns for investing in capacity and/or quality which could reduce drug shortages.

Another study of GPOs and antitrust policy conducted as a result of interest by the US Department of Justice and Federal Trade Commission regarding the extent of market power among some large GPOs and potential anticompetitive effects, analyzed the degree to which markets in which large GPOs operated were characterized more by monopsony (single buyer) than competitive markets.[19] As described in the section on market structure, there is significant concentration in market share among a few pharmaceutical GPOs from their ability to aggregate large numbers of members into one purchasing bloc. Concerns over such a degree of market power include the potential to reduce the number of suppliers of drug products through contracting provisions such as "sole source contracts," or minimum volume requirements as well as extracting substantial discounts from manufacturers to lower costs to their members but may also reduce manufacturer incentives to invest in quality. The study's authors conclude that large GPOs are more reflective of procompetitive behavior in that their size at first glance may appear to limit supplier access to GPO members, but in actuality it may not be the case since suppliers have an opportunity to compete for a contract.

The data and previous literature support the assertion of this study that the pharmaceutical product market generally exhibits market imperfections that may be reflected in a number of economic models. As a result, several models are introduced to explain the behavior of buyers and sellers of pharmaceutical products and assess the impact of manufacturing quality ratings on manufacturer incentives to invest in quality.

A baseline model is presented as a means of benchmarking other model outcomes. This model is referred to as the quasi-competitive economic model. This model is compared alongside other models featuring a less competitive environment among buyers and sellers including oligopolistic/monopolistic competition (few or single sellers), and oligopsonistic/monopsonistic competition (few or single buyers). Extensions to these models are made to incorporate production uncertainty and to model market participant reactions to equilibrium outcomes dynamically from introduction of a manufacturing quality rating system.

Of some interest to this analysis is the role pricing could play to incent manufacturers to invest in quality processes and controls beyond CGMP standards. The degree to which

pricing could influence such outcomes depends in large measure on the price sensitivity or elasticity of demand for pharmaceutical products. In economics, the own elasticity of demand (ε) for product q refers to the proportionate rate of change in the demand for that product for a proportionate change in price (p) of product q. This can be expressed mathematically as the following:

1. $\varepsilon = \dfrac{p \partial q}{q \partial p}$

Since most products have an inverse relationship between price and quantity demanded, products are deemed to be price inelastic when $\varepsilon > -1$ and elastic whenever $\varepsilon < -1$. Products with inelastic demand are often thought of as necessities, e.g., physician prescribed pharmaceutical products while products with elastic demand are typically thought of as discretionary products. Required consumer copayments for drug products under insurance plans are also a contributing factor for inelastic demand along with the need for the drug product by the consumer. A significant amount of empirical analysis has developed over the years estimating the elasticity of demand for pharmaceutical products. For example, Gatwood found that across a number of different drug products, elasticities ranged from -.02 to -.16.[20] To illustrate the interpretation of an elasticity of -.10, it implies that a 1% increase in price would result in a .1% decline in quantity demanded. Evidence of inelastic demand for pharmaceutical products has been identified as one factor explaining the occurrence of drug shortages.[21]

One of the issues with many of these empirical studies is that the derived elasticity estimates represent only one aspect of the total picture of pharmaceutical product demand elasticity. Specifically, Yueng et al., raise the issue that a more complete picture of elasticity emerges only after taking into account the total elasticity which includes not just the own (or product-specific) elasticity but also the cross-product elasticities of substitute products as well.[22] In their study, Yueng et al., found increasing elasticity by consumers for drug products in "increasing copayment tiers." The implication of that finding for this analysis is 1/ there is some variability among drug products in elasticity and 2/ there may be some potential to explore modifications to pharmaceutical formulary plans to steer demand taking into account some benefit from a quality rating on a product.

Typically, such formulary plans feature a tiered system, whereby higher acquisition cost drug products appear on a higher tier than lower cost products. Consumers are then incented to use lower cost drugs based on this tiering that also reflects the copayments and/or cost-sharing rates of these products. While such cost-based tiering methods have been in place for years, value-based formulary plans are designed to broaden product tiering criteria beyond cost to include other benefits to the consumer such as effectiveness of the medication, and side effects. One of the implications from the study by Yeung et. al on manufacturing quality ratings is their analysis that increasing the price of a low value drug raises the demand elasticity under a value-based versus a cost-based formulary plan which incents consumers to lower their demand for that drug product. Incorporating a component of a value-based formulary plan design to account for accessibility and/or quality might raise consumer awareness regarding drug products toward differentiating drugs based on manufacturing ratings. In the use case section, some discussion of product quality ratings effects on differentiating consumer demand will be presented.

PHARMACEUTICAL MARKET IMPERFECTIONS AND IMPLICATIONS FOR MANUFACTURING QUALITY

The federal Drug Shortage Task Force cited the pharmaceutical "market's failure to recognize and reward quality management maturity." [23] Implementation of a manufacturing quality rating system is intended to elevate market participants' awareness of potential differences in manufacturing quality for a particular drug product. The pharmaceutical market today thus reflects information asymmetry regarding quality manufacturing, and thus the existence of a potential market failure. Information asymmetry refers to a condition where one party to a transaction possesses more information than the other that results in imperfect market pricing. This market condition was famously described by Akerlof, in his Nobel Prize work on the market for used cars.[24] Akerlof contended that certain markets exhibit information asymmetries where buyers of used cars lack information regarding the quality of the car they are buying. The dealer, in contrast possesses more information on the car's history including maintenance and accidents.[25] In Akerlof's model, since buyers are unable to discern differences in the quality between used cars, they will pay an average price for a good or poor quality used car which has implications for the quality of used cars that ultimately come to market and the manner in which pricing of used cars does not properly account

for actual differences in quality. This lack of information by buyers leads to adverse selection in the market whereby higher quality used cars leave the market and sellers desire to sell only "lemons" since the price of the lemon is lower than the average market price for used cars. One of the criteria for this model to exist is a deficiency in public policy to provide product quality guarantees to the market.

Although the FDA's "safe and effective" standard for pharmaceutical products provides a minimum threshold of product quality for consumers and industry, it has to a large degree served to promote a lack of product differentiation on the basis of manufacturing quality differences beyond the CGMP standards which could be a contributing factor to drug shortages. It is presumed that FDA's implementation of a quality rating system under its QMM program would begin to correct for this information gap and promote a market mechanism that reduces this potential market failure and leads to improved investments in manufacturing quality.

ECONOMIC SCENARIOS WITHOUT PRODUCT DIFFERENTIATION

As a means of comparison with alternative market configurations, including one where a manufacturing quality rating is imposed on the market, a quasi-competitive market is adopted. This market focuses on a single drug product where for ease of exposition, two sellers (manufacturers 1 and 2 (M1 and M2) produce the same drug product.[26] The model assumes due to the presence of only two sellers with differing levels of manufacturing quality that market imperfections exist which affect equilibrium price (P) and output (Q). The market is characterized by a lack of product differentiation, implicitly assuming no quality rating system exists for buyers to distinguish between the two manufacturers on the basis of quality. Consequently, both sellers face a single demand curve defined as the following:

2. $P = F(Q_1 + Q_2)$

where Q_1 and Q_2 are the quantity of drug products manufactured by M1 and M2, respectively. Further, manufacturer profitability (Π_i) is defined as;

$3a.\ \Pi_1 = Q_1[F(Q_1 + Q_2) - C_1(Q_1)]$
$3b.\ \Pi_2 = Q_2[F(Q_1 + Q_2) - C_2(Q_2)]$

where $C_1(Q_1)$ and $C_2(Q_2)$ are the cost functions of M1 and M2 in producing the drug product. Market equilibrium is determined as follows:

4a. $P = F(Q_1 + Q_2) = C_1'(Q_1)$ and

4b. $P = F(Q_1 + Q_2) = C_2'(Q_2)$

where C'_1 and C'_2 are the marginal costs (MC) for M1 and M2, or

5. $\dfrac{\partial C_1}{\partial Q_1} = C_1'$ and $\dfrac{\partial C_2}{\partial Q_2} = C_2'$

In solving equations 4 and 5 for Q_1 and Q_2, there is a relationship between both outputs defined as $Q_1 = f_1(Q_2)$ and $Q_2 = f_2(Q_1)$. A graphical representation for a quasi-competitive drug market is found in Figure 3.

In the left graph, equilibrium is determined by the intersection of both marginal cost curves with demand (price) at Q^*_1 and Q^*_2 and P^*. Accordingly, the solution for Q^*_1 and Q^*_2 are noted by the intersection of the two seller reaction functions in the right graph. To reinforce the dynamics of this quasi-competitive solution, consider the following numerical analysis.

A set of demand and cost functions are presented with parameterizations set such that annual production levels of at least one manufacturer comparable to a large facility producing 2,000 tons of tablets per year.[27] These parameter settings will be fixed for all other economic scenarios and numerical analyses that follow for comparative purposes. Demand is defined as:

6. $P = \alpha - \beta(Q_1 + Q_2)$

Similarly, cost functions for M1 and M2 are given as:

7a. $C_1 = \delta_1 + \chi_1(Q_1)$

7b. $C_2 = \delta_2 + \chi_2(Q_2)^2$

In the specification of costs above it is assumed that M2, due to process inefficiencies from a lack of investment in manufacturing quality practices, has a higher cost structure than M1.

Equilibrium levels of Q_1 and Q_2 are found as the following:

$$8a. Q_1^* = \frac{\alpha - \beta Q_2 - \chi_1}{\beta}$$

$$8b. Q_2^* = \frac{\alpha - \beta Q_1}{\beta + 2\chi_2}$$

Table 3 contains the model parameters and Table 4 the model results.

Model parameters were optimized using a linear programming technique that assured that the profit margins of a high-quality manufacturer M1 and lower quality manufacturer M2 were 15 and 5 percent, respectively. The differences in profitability reflect the effect of lower costs due to process improvements by M1 (or, alternatively higher costs of M2). Those profit margins were designed to represent differential profitability reflecting the relative impacts of poor-quality manufacturing on increasing the inefficiency and costs associated with producing the drug product as compared with M1.

Figure 3 Equilibrium in a Quasi-Competitive Drug Product Market
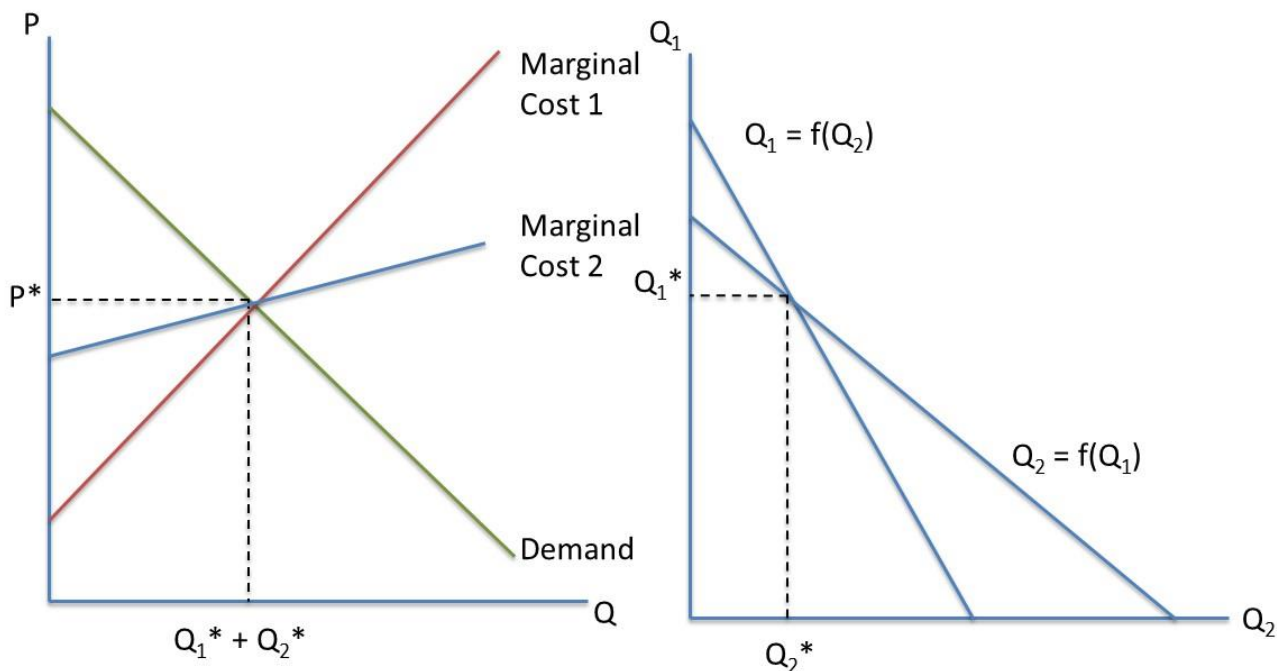
Table 3 Numerical Model Parameters

Parameter	Value
α	28.4
β	.002
χ_1	17.9
χ_2	.01
δ_1	0
δ_2	9,891

The results from this numeric analysis of a quasi-competitive market establish the baseline economic scenario for a market with two sellers. As established by the parameterization, M1 produces more than twice the amount of the same drug product as M2 and enjoys a much larger dollar-based profit as a result.

Table 4 Numerical Model Results

Factor	Result
Q_1	2,119
Q_2	1,005
P	$21.83 ($000s)
$Profit_1$	$8,331 ($000s)
$Profit_2$	$1,954 ($000s)
Profit Margin M1	18%
Profit Margin M2	8.9%
C_1	$37,942 (000s)
C_2	$20,017 (000s)

Now assume that the market is not as competitive as the quasi-competitive scenario presented. A classic economic representation of market imperfections with few sellers (in this case 2) is the Cournot duopoly. As before we assume no product differentiation in

this market, i.e., no manufacturing quality rating scheme. Each manufacturer's objective is to maximize their profit with respect to their production assuming that what they produce is unaffected by the other manufacturer's production decision. This can be represented as the following:

9a. $\frac{\partial \Pi_1}{\partial Q_1} = 0$

9b. $\frac{\partial \Pi_2}{\partial Q_2} = 0$

Leveraging the parameters from the quasi-competitive scenario, it can be shown that for Q_1 and Q_2:

10a. $Q_1^* = \frac{\delta_1 - \alpha + \beta Q_2}{2\beta}$

10b. $Q_2^* = \frac{\delta_2 - \alpha + \beta Q_1}{2\beta + 2\chi_2}$

The results of the numerical analysis comparing the Cournot duopoly scenario are shown in Table 5 and a graphical analysis is depicted in Figure 4 of the Cournot duopoly scenario. The Cournot duopoly scenario manufactures less total product than the quasi-competitive scenario, at a higher price and larger profits. This suggests in situations that do not follow standard competitive market equilibrium conditions where P = MC, segments of the pharmaceutical product market where few sellers exist can yield a supply of product that is at sub-competitive levels. Note that in Figure 4, each manufacturer's reaction function is shown on the right. Each manufacturer's reaction function describes the level of their drug production as a function of the other's output. In other words, for any value of Q_2, for example, the corresponding level of Q_1 maximizes M1's profit. In this case, the intersection of the two reaction functions at Q_1 = 2,000 tons/year and Q_2 = 1,000 tons/year correspond to the diagram on the left in Figure 4 where the two marginal cost curves for M1 and M2 intersect with demand. Markets for drug products with few sellers as characterized by a Cournot duopoly scenario could accentuate drug shortages when they occur due to a lack of manufacturing diversification and capacity limitations. Ensuring a high level of manufacturing quality for such market segments that have potentially more vulnerability from a shortage than a more competitive market would

help mitigate risk. A manufacturing quality rating, by extension might be of greater consequence for less competitive markets.

Table 5 Quasi-Competitive vs Cournot Duopoly Scenario Analysis: No Product Differentiation

Market Variable	Quasi-Competitive	Cournot Duopoly	Percent Difference
Q_1 (tons/year)	2,119	2,000	-5.62
Q_2 (tons/year)	1,006	1,000	-.6
P ($/ton)	$21.83	$22.1	1.24
Profit M1 ($000s)	$8,331	$8,389	.7
Profit M2 ($000s)	$1,954	$2,206	12.9
Revenue M1 ($000s)	$46,273	$44,194	-4.49
Revenue M2 ($000s)	$21,971	$22,097	.6
Cost M1 ($000s)	$37,942	$35,806	-5.63
Cost M2 ($000s)	$20,017	$19,890	-.6
Profit Margin M1 (%)	18	18.9	5.44
Profit Margin M2 (%)	8.9	10.0	12.26

ECONOMIC SCENARIOS WITH PRODUCT DIFFERENTIATION

As described in the previous section, both the quasi-competitive and Cournot duopoly scenarios were presented under conditions where for a particular drug product, there was no observable differentiation by buyers between Q_1 and Q_2. In this section, a manufacturing quality rating system is imposed on both manufacturers. Establishing a quality rating provides buyers with a mechanism now to distinguish between Q_1 and Q_2 on the basis of a scoring system that empirically measures quality differences between M1 and M2 above CGMP requirements. As a result, M1 and M2 each face different demand curves and price (P_1 and P_2 for M1 and M2, respectively). A quality rating thus would introduce a critical change in the drug product's market equilibrium conditions. To illustrate the effect of a quality rating for manufacturers of a drug product in a less-competitive market, a Cournot duopoly structure is used.

Figure 4 Cournot Duopoly Equilibrium Output and Price – No Product Differentiation
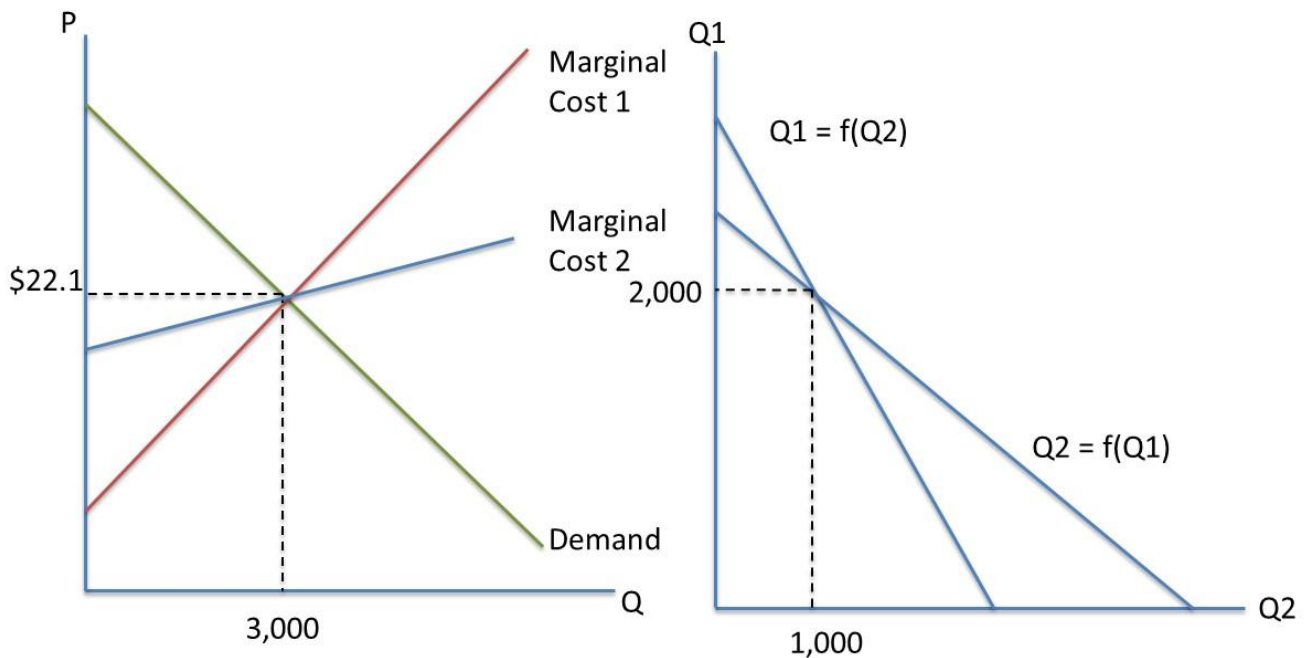
In this scenario, both M1 and M2 as before maximize profit but now take into account their different demand curves. The demand functions for each manufacturer are as follows:

$$11a. P_1 = \alpha_1 - \beta_1(Q_1 + Q_2)$$
$$11b. P_2 = \alpha_2 - \beta_2(Q_1 + Q_2)$$

The cost functions for both M1 and M2 are given as:

$$12a. C_1 = \delta_1 + \chi_1(Q_1)$$
$$12b. C_2 = \delta_2 + \chi_2(Q_2)^2$$

where δ_1 and δ_2 represent fixed costs and X_1 and X_2 are variable costs of production. Profit is further defined based on these demand and cost functions as:

$$13a. \Pi_1 = Q_1(\alpha_1 - \beta_1(Q_1 + Q_2)) - (\delta_1 + \chi_1(Q_1))$$

13b. $\Pi_2 = Q_2\big(\alpha_2 - \beta_2(Q_1 + Q_2)\big) - (\delta_2 + \chi_2(Q_2)^2)$

Accordingly, market equilibrium is established as the following:

14a. $\dfrac{\partial \Pi_1}{\partial Q_1} = \alpha_1 - 2\beta_1 Q_1 - \beta_1 Q_2 - \chi_1 = 0$

14b. $\dfrac{\partial \Pi_2}{\partial Q_2} = \alpha_2 - 2\beta_2 Q_2 - \beta_2 Q_1 - \chi_2 2Q_2 = 0$

A comparison of the results from the numerical analyses between markets with and without product differentiation for a Cournot duopoly is presented in Table 6. The introduction of a manufacturing quality rating has a significant effect on market equilibrium outcomes and thereby incentives for manufacturers to invest in quality processes when such a rating system is fully implemented and used by all buyers and when demand is elastic to illustrate the full effect of a rating. Potential market and implementation constraints of a rating's impact will be explored in a later section.

Under the production differentiation scenario, price for the better quality manufacturer goes up from $22.1 to nearly $31 while price falls from $22.1 to $19 for the lesser quality manufacturer. Moreover, compared to the no product differentiation scenario, output for M1 rises but falls for M2. M1 is significantly more profitable and M2 less so in a market where the drug products of both manufacturers are differentiated by manufacturing quality.

Introducing a quality rating reduces the information asymmetry problem regarding manufacturing quality differences that exists today for pharmaceutical product buyers and their members or customers which is reflected by differential pricing for manufacturers whereby higher quality manufacturers are rewarded with higher prices (essentially reflecting a premium for quality) and lower quality manufacturers receive lower pricing reflecting a cost of quality.

Profitability is thus higher for M1 and lower for M2. A quality rating under this scenario would provide an incentive to invest in quality manufacturing processes. Specifically, pricing improves as does profitability for a higher quality manufacturer. The lesser quality manufacturer is placed in a less competitive position vis a vis M1 and faces two

choices; invest in quality to firm up their competitive position or over the long-term face exiting the market altogether. The latter choice could lead to outcomes that could amplify drug shortages by removing manufacturing capacity from the market assuming other competitors are operating at full or near full capacity.

Table 6 Comparison of Results for Cournot Duopoly with and without Product Differentiation

Market Variable	Product Differentiation	No Product Differentiation	Percent Difference
Q_1 (tons/year)	2,138	2,000	6.9
Q_2 (tons/year)	651	1,000	-34.9
P_1 ($/ton)	$30.92	$22.1	39.9
P_2	$19.58	$22.1	-11.4
Profit M1 ($000s)	$27,825	$8,389	231.7
Profit M2 ($000s)	-$1,383	$2,206	-162.7
Revenue M1 ($000s)	$66,089	$44,194	49.5
Revenue M2 ($000s)	$12,748	$22,097	-42.3
Cost M1 ($000s)	$38,264	$35,806	6.9
Cost M2 ($000s)	$14,131	$19,890	-28.9
Profit Margin M1 (%)	42.1	18.9	122.8
Profit Margin M2 (%)	-10.8	10.0	-208.0

There could be two countervailing effects from (capacity and quality investment) from remaining firms in response to an exit by a low-quality manufacturer. One possibility is that higher quality firms, enjoying higher prices and extranormal profitability could expand production capacity to fill demand and over time fulfill equilibrium output lost by the exit of the lower quality manufacturer. That outcome could mitigate future shortages by production from high quality firms. Of course, a caveat to this outcome is the time required to build capacity.

Suppose that lower-quality manufacturer M2 decides to invest in quality processes over the next period following the introduction of a manufacturing quality rating system and the resulting effect observed on its product price and output. This investment is further

assumed to raise M2's cost structure from the previous scenarios by 10 percent. Another assumption is that following the quality investment by M2, the new quality rating for M2 is the same as for M1. In that case, both M1 and M2 face the same demand function as under the Cournot duopoly scenario with no product differentiation. The results of a numerical analysis using all other parameters used in the previous analysis for demand and cost (adjusting M2's cost parameters upward by 10 percent) are shown in Table 7.

Table 7 Comparison of Results for Cournot Duopoly with and without Product Differentiation after Quality Investment by M2

Market Variable	M2 Raises Quality to M1 Rating	No Product Differentiation	Product Differentiation
Q_1 (tons/year)	2,039	2,000	2,138
Q_2 (tons/year)	920	1,000	651
P_1 ($/ton)	$22.1	$22.1	$30.92
P_2	$22.1	$22.1	$19.58
Profit M1 ($000s)	$8,725	$8,389	$27,825
Profit M2 ($000s)	$1,096	$2,206	-$1,383
Revenue M1 ($000s)	$45,243	$44,194	$66,089
Revenue M2 ($000s)	$20,416	$22,097	$12,748
Cost M1 ($000s)	$36,517	$35,806	$38,264
Cost M2 ($000s)	$19,319	$19,890	$14,131
Profit Margin M1 (%)	19.3	18.9	42.1
Profit Margin M2 (%)	5.4	10.0	-10.8

Under this dynamic scenario, M2's profitability, output and pricing improve from under the product differentiation scenario. Note that by investing in quality, M2's costs rise which creates a drag on profit. Over time, the company's cost structure could decline if the investment yields production efficiencies which could be expected due to implementation of processes and controls that reduce production stoppages, product defects and increases automation.

PRODUCTION UNCERTAINTY AND QUALITY RATINGS

All the economic scenarios have assumed production certainty for both M1 and M2. In this section that assumption is relaxed. Production plant operations are subject to a number of possible events that can shut down operations in full or partially depending on the nature and severity of the event. Events could include the inability to source raw materials, worker shortages (e.g., Covid-19), product contamination, mechanical breakdowns, manual handling errors and other process or system issues. To frame this discussion in economic terms, it is assumed that M2 faces production uncertainty while M1 does not. This will permit an examination of the effect of uncertainty on a single producer without loss of generality for all manufacturers. Consistent with expected utility analysis, M2 is assumed to have a utility function; $U_2(\Pi)$ where Π represents M2's profit and M2 follows the von Neumann-Morgenstern axioms under uncertainty. In this example, M2's price is fixed and has a target level of production (contracted level with a set of buyers) of Q^*_2. The actual level of production can vary from Q^*_2 based on any number of events described above. The set of n possible output levels is described as ($k_1 Q^*_2$...., $k_n Q^*_2$) where k_i represents some fraction of target output for production event i that occurs with probability p_i.

M2 is assumed to maximize their expected utility of profit as follows:

15. $E[U_2(\pi)] = \sum_{i=1}^{N} p_i U[P_2 k_i Q_2^* - C_2(Q_2)]$

Equilibrium is established by the following condition:

16. $\frac{\partial E[U_2(\pi)]}{\partial Q_2^*} = \sum_{i=1}^{N} p_i U'(\Pi_2)[P_2 k_i - C_2'(Q_2^*)] = 0$

Further, it is assumed that the target levels of output for M1 and M2 are those following the no product differentiation Cournot duopoly scenario of 2,000 and 1,000 tons/year, respectively and that there is a 5% chance of a shortage for M2 and shortage amounts are uniformly distributed.

A shortage for M2 is defined then as Q^*_2 - Q^i_2 where Q^i_2 represents the level of Q_2 under simulated trial i (event). For each k_i, a random variable between 0 and 1 is drawn one thousand times. The expected level of Q_2; $E(Q_2)$ is defined as:

$$17.\ E(Q^*_2) = .95(Q^*_2) + .05 \sum_{i=1}^{1,000} (Q^*_2 - Q^i_2) * \frac{1}{1,000}$$

Based on the model's inputs from earlier, $E(Q_2)$ equals 974 tons and the expected shortage would be 26 tons. The average shortage over the thousand scenarios would be approximately 470 tons (for just the 5% of the scenarios that could occur). Expected profit for M2 can be defined as the following:

$$18.\ E(\pi_2) = .95 * \pi^*_2 + .05 \sum_{i=1}^{1,000} \pi^i_2 * \frac{1}{1,000} = \$2,031$$

Expected profit for M2 is about 8 percent lower than under certain production and profit margin also declines from 10% to 9.3%. The erosion in profitability hinders M2's ability to address quality issues in the absence of a quality rating. The implementation of a quality rating system, however, by differentiating demand for M1 and M2 output based on quality differences would be expected to have a similar effect on incenting investment in quality by M2 as was described under the production certainty scenario.

ALTERNATIVE MARKET SCENARIOS

To this point the market scenarios presented focused on quasi-competitive or oligopolistic markets but beyond these there are others worth considering as they can apply to other segments of the pharmaceutical market. These include markets for products that deviate from standard competitive market conditions on either the demand or supply side in different ways from a model of few sellers such as the Cournot duopoly. In the drug shortage data analysis conducted for this study, 13% of drug products in shortage had one applicant (Table 2). These drug products were split between brand and generic drug products. In such cases neither of the previous scenarios appropriately characterizes market equilibrium for these products and so examination of monopolistic market conditions is warranted. Likewise, given market concentration among GPOs and PBMs, the potential for demand-side market imperfections exists. In such case, monopsonistic

(one buyer) or oligopsonistic (few buyers) may affect market equilibriums in ways that deviate from prior market scenarios. Finally, consideration of government markets for prescription drugs such as Medicare, Medicaid and the Veterans Administration (VA) is presented in this section in terms of how a manufacturing quality rating could impact market equilibrium and manufacturer incentives to invest in quality should such a rating be applied in these areas.

MONOPOLY MARKETS AND QUALITY RATINGS

Standard economic theory of monopoly establishes that a monopolist sets marginal revenue (MR) equal to marginal cost (MC) rather than as observed under the quasi-competitive scenario that followed the perfect competition equilibrium of price equal to MC. Figure 5 shows that under monopoly conditions, the manufacturer produces less

Figure 5 Monopoly Versus Competitive Market Equilibria
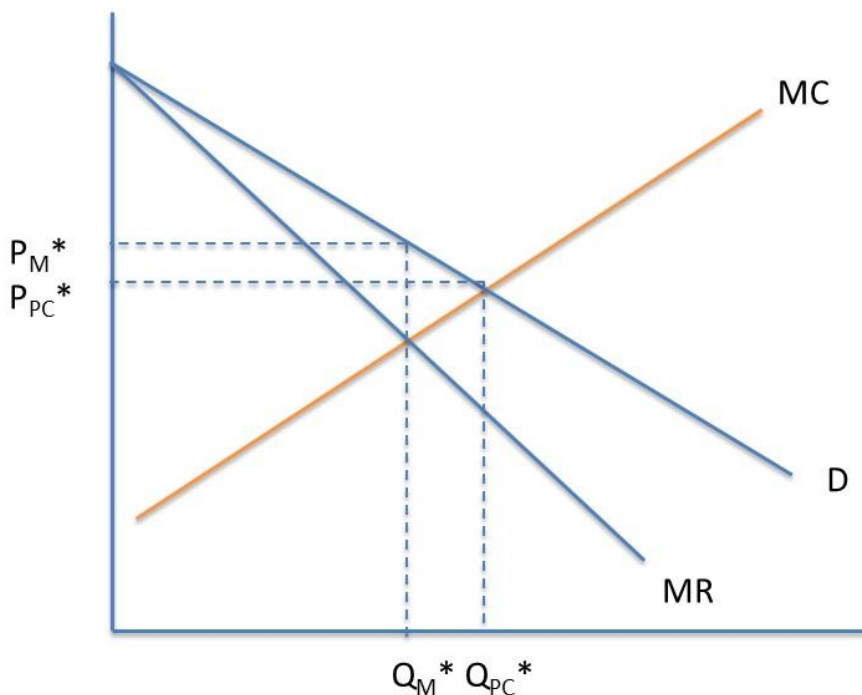
output than under perfect competition (i.e., $Q^*_M < Q^*_{PC}$) and at a higher price (i.e., $P^*_M > P^*_{PC}$). This is consistent with the pharmaceutical market for brand products where much higher pricing of such pharmaceuticals is observed. The market power of the manufacturer under these conditions is significant, even in the face of strong market power by a large GPO or PBM. The ability of buyers to negotiate lower prices and or

higher rebates and other concessions is limited. In such a market the impact of a manufacturing quality rating would also be limited. Lacking an alternative supplier of that drug, a buyer leveraging a quality rating in negotiating a contract with a monopolist manufacturer would find it to be of limited utility in affecting price. This can be seen in Figure 6. The market equilibrium without a quality rating is shown at Q^*_1 and P^*_1 using marginal revenue and demand curves MR and D. If we assume that after a quality rating has been implemented that the demand curve shifts downward to D' (reflecting a poor rating), the marginal revenue curve would shift down to MR'. In such a circumstance, the manufacturer's response would be to shift production to Q^*_2 and price to P^*_2. However, the buyer's members or customers require the target level of output Q^*_1. Instead of accepting a lower output, the buyer will accept the original level of output and price, hence rendering the quality rating of no value in affecting price.

MONOPSONY MARKETS AND QUALITY RATINGS

Clearly from the section on the market structure of the pharmaceutical industry, over the years a significant concentration among large pharmaceutical product buyers has emerged, providing some market power to healthcare providers and pharmacies by virtue of aggregating the demand for pharmaceutical products among their members or customers. Up to this point the analysis assumed that pharmaceutical markets were characterized by many buyers, and while technically that may be the case, the degree of market concentration by a few large GPOs and PBMs requires some consideration in terms of the impact quality ratings would have on such a market dynamic. Under a classic monopsony model, a single buyer maximizes profit at the point where marginal revenue product (demand) equals marginal cost. This is depicted in Figure 7. In this example, a single buyer, e.g., a GPO, with some degree of market power would settle on a level of output Q^M (lower than the competitive market level) and at a lower price P^M than the competitive market. However, as argued by Blair and Durrance, a monopsonist pharmaceutical buyer such an equilibrium is largely infeasible, again due to the buyer's member or customer needs for a level of product supply greater than the optimal monopsonist level.[28] One way that a monopsonist buyer could potentially affect pricing is via an all-or-nothing contract.[29]

Such contracts would only be practical for drug products with multiple manufacturers. The market equilibrium in this case is shown in Figure 8. Here, the monopsonist requires

the target level output Q*, however, by way of its market power forces the manufacturer to a different supply curve S^A with price P^A, and thus eliminating the manufacturer's surplus shown in the blue triangle. This tactic could apply in a situation where a monopsonist buyer leverages a quality rating with a manufacturer that turns out to have a rating indicating below average quality and other supply alternatives exist. In such a

Figure 6 Monopoly Under Quality Rating System
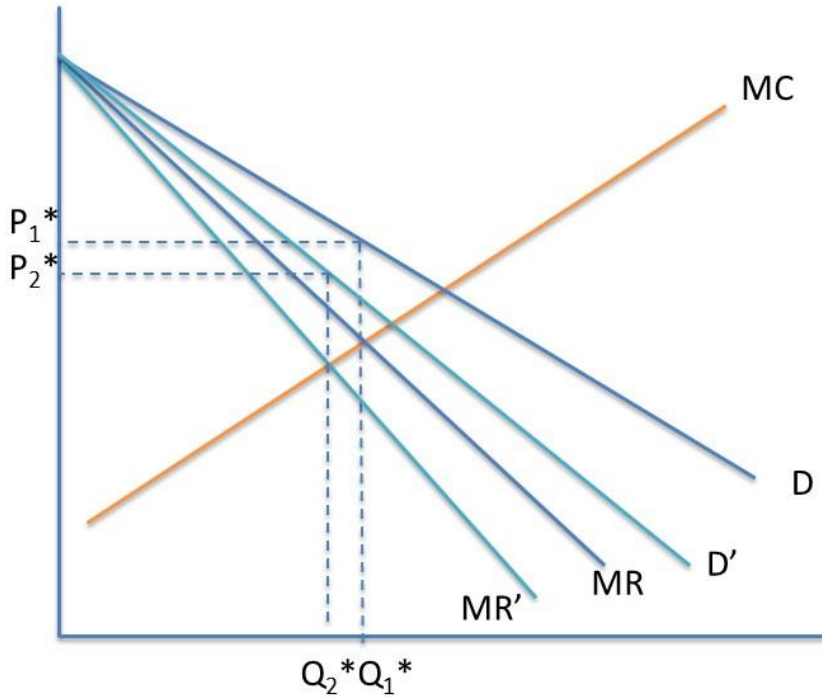
case, an all-or-nothing strategy could be used to drive prices lower based on the market power of the buyer, and the competitiveness of that particular product on the supply side. Such an outcome could incent the manufacturer to invest in quality processes to recoup part of their lost producer surplus. However, a potential downside effect as Blair and Durrance note from such a strategy would be to reduce incentives for companies to invest in drug product research and development as the all-or-nothing strategy reduces the returns from such investments.

To this point the study has omitted any discussion of how a quality rating system could affect prescription drug products in federal healthcare programs such as Medicare, Medicaid and VA. Under the Medicare Part D prescription drug plan, Medicare does not negotiate prices with manufacturers based on a "noninterference" clause in the legislation establishing Part D.[30] Under Part B, Medicare reimburses healthcare providers based on the ASP when that is available or wholesale acquisition cost (WAC) when it is unavailable.

Figure 7 Monopsony Market Equilibrium without a Quality Rating System
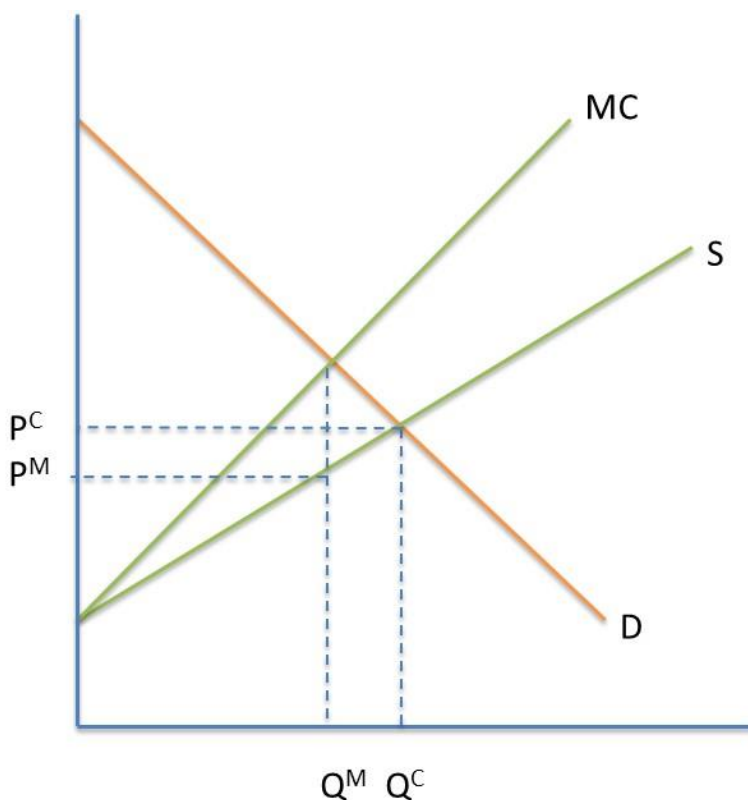
In the case of Medicaid, manufacturers with drug products included under the program are required to provide rebates to the federal government. In the case of VA, ceiling prices and minimum discounts are used to manage drug prices. To gain a perspective on how a federal program relates to the healthcare supply chain, consider Figure 9. In this representation, the GPO or buyer, negotiates price as in the private market with Medicare

reimbursing healthcare providers and premiums being received by Medicare from patients.

The impact of a quality rating system for manufacturers providing products to federal drug programs would vary based on how the market works today. In the case of Medicare Part D, a quality rating effect would be transmitted via the private purchasing organization given the noninterference clause. A similar result would be expected under Part B again since Medicare does not negotiate pricing for that program. So, in this case, the effect on manufacturing quality would depend on the type of market reflected by the

Figure 8 Monopsony Market Equilibrium Under an All-or-Nothing Contract
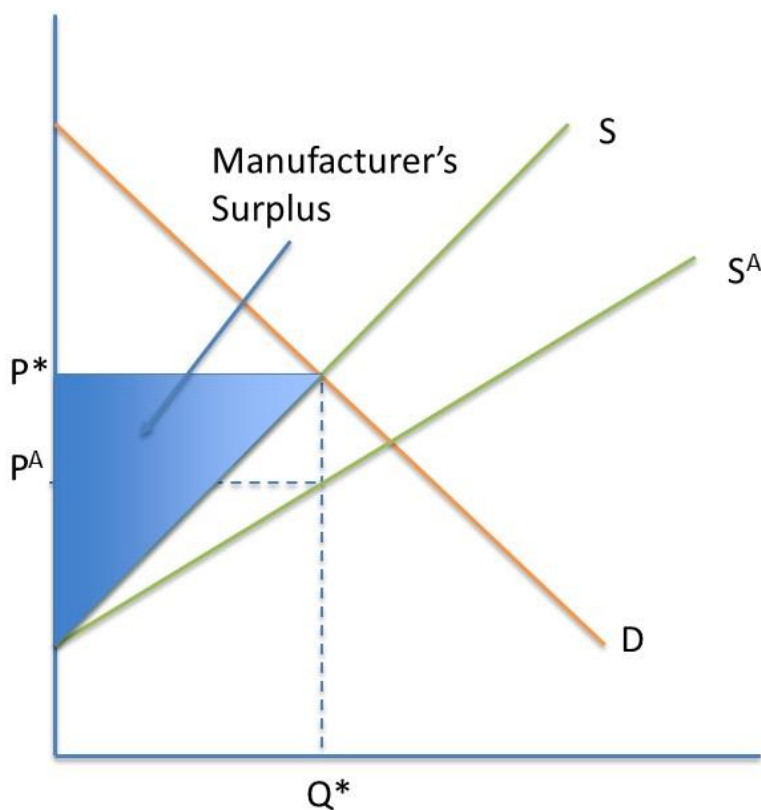
drug product, e.g., quasi-competitive. Echoing an Executive Order issued early in his Administration, President Biden, in his 2022 State of the Union Address called again for legislators to allow Medicare to negotiate price with manufacturers.[31] Such a proposal could also facilitate the use of a quality rating process if adopted by Medicare in price negotiations.

For Medicaid, the federal government requires manufacturers to rebate a portion of drug payments to the government. And a number of states also negotiate rebates with manufacturers. In theory, such a rebate program has elements resembling the monopsonist market but with a twist. Pharmacies procure their drug products from manufacturers leveraging purchasing organizations when in their best interest. But because of the size of the Medicaid program, a quality rating system could be used by Medicaid to extract larger rebates from poorer quality manufacturers, similar to a monopsonist's all-or-nothing strategy in reducing manufacturer surplus for a target level of output. This might also be possible under the VA drug program as part of their overall assessment process. And as discussed earlier, a lower quality manufacturer conceding larger rebates in part reflecting a below average quality rating could incent the manufacturer to invest in quality to lower those rebates in the future.

Figure 9 Healthcare Supply Chain Under Medicare Part B Plan
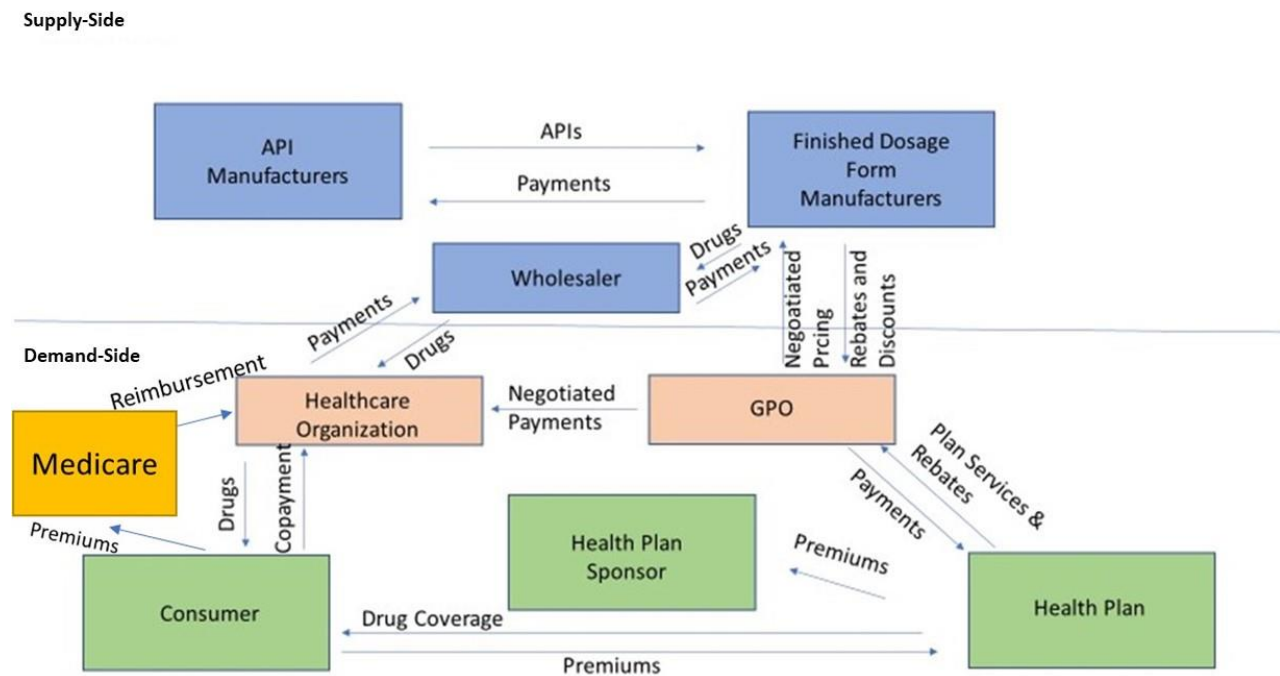
SUMMARIZING THE MARKET SCENARIO ANALYSIS ON MANUFACTURING QUALITY RATINGS

The pharmaceutical product market is characterized by the following features that have important implications for the effectiveness of a manufacturing quality rating system to incent investment in quality:

- The lack of a quality rating system in pharmaceutical markets creates a classic information asymmetry problem in the market, resulting in an inability by buyers to distinguish one manufacturer from another for a particular drug product. This explains the market's mispricing of manufacturing quality.

- Different types of participants on both the demand and supply side of the market inherently create an environment that reduces the attention and collective support required to negotiate contracts that incent manufacturers to invest in quality. On the demand side, consumers or patients, when drug product substitutes are available, may not feel the effect of a quality-related manufacturing event in the short-term as their healthcare provider or pharmacies substitute out those products. The health plans and sponsors through which consumers enroll for healthcare including prescription drug plan services, while having significant market presence, are relatively immune from the impacts of a manufacturing quality event. The cost of a drug shortage is largely borne by healthcare providers and pharmacies, but they are not in many cases directly negotiating with wholesalers or manufacturers.

- High degree of concentration of GPOs and PBMs on the demand side can exert market power in some cases to the benefit of their members or customers, but it is product specific and dependent upon the degree of competition for that product (i.e., number of manufacturers) and availability of viable substitute products. Rebates or discounts on drug products negotiated by drug purchasing companies do not appear to reflect any quality-related adjustments and thus there is currently a disconnect in the way in which the market operates to properly reflect such quality-related costs in drug pricing.

- The supply side of the market is characterized by a varying degree of competitiveness that affects product equilibrium pricing and output levels. A sizable percentage of drug products have a single seller, creating a monopolistic market while another significant portion of the market has few sellers, leading to a

type of oligopolistic competition. Another large segment of drug products are sold in markets characterized by a relatively high degree of competition.

- The importance of drug products to consumers and patients for improving their health places these products in economics terms as necessities rather than discretionary goods. As a result, own price elasticities of demand tend to be inelastic. This characteristic ultimately reduces the pricing mechanism to be a primary conduit for incenting manufacturers to invest in quality. Some quality adjustment to price could be obtained following implementation of a quality rating system but would be expected to be small based on empirical research on price elasticity in this market. Quality ratings may have more of an impact on incenting manufacturing quality when tied to drug formulary placement negotiations.

ANALYSIS OF DRUG MANUFACTURER CHARACTERISTICS AND THEIR IMPACT ON DRUG SHORTAGES

The preceding economic analysis highlighted a number of features characterizing pharmaceutical product markets. These include the degree of competition for a specific drug product and associated market power. Beyond those factors lie other attributes that may explain relative differences in manufacturing quality. This section surveys these factors, discusses their potential effect on the drug supply chain and presents an empirical analysis of their effect on drug shortages.

It is hypothesized that deficiencies in manufacturing quality may manifest in some disruption of the drug product supply chain. The feedback mechanism for such an outcome is presented in Figure 10. Delivery of a sufficient, continuous level of drug product to market is dependent on the level of investment in manufacturing quality and external risks or events that could unexpectedly affect that supply. The level of investment in manufacturing quality in turn is dependent on a number of financial enablers/disablers.

Financial enablers/disablers include the degree of market competition for a drug product, the profitability of the company overall, the returns on the drug product and associated return on investment from quality processes and technology. A number of factors affect company and product profitability and returns including the degree of competition in the

market, market demand, whether the drug is a brand or generic product, operational cost efficiency, and product diversification, among others.

The level of quality investment by API or FDF manufacturers defines a number of process enablers/disablers to supply quality and continuity. This includes the age of plant and equipment as well as the level of technology and production automation. Older, less technologically advanced and more manual production processes would be expected to be more prone to a manufacturing disruption at some point. Other potential factors could include how well the manufacturer monitors the production process and the degree of complexity associated with the product. Products, for example with more complex molecules may require more attention to the manufacturing process and steps to ensure product uniformity and adherence with FDA standards than simpler pharmaceutical products.

Beyond manufacturer-specific quality enablers/disablers to product supply continuity are a host of external events that could create unexpected disruptions on the supply chain of an individual API or FDF manufacturer or on multiple manufacturers. The Covid-19 pandemic provides a recent example of such an external event; however, geopolitical and even climatological risks can disrupt pharmaceutical supply chains. Building resiliency or redundancy into the manufacturing process can reduce the risks of such external as well as unexpected manufacturer specific supply disruptions. Of some concern today is that pharmaceutical manufacturing operates at levels near full capacity. This implies that when a disruption by an API or FDF manufacturer occurs, that slack would need to be taken up by the other producers if they exist to avoid a shortage. Many drug products operate in highly competitive markets such as generics that reduce profit margins and therefore limit the amount of capital that can be allocated to manufacturing quality investments. It may also be the case that management biases toward investments resulting in direct short-term profitability and away from those that may require a longer payback period to realize target returns factor into manufacturing quality investment decisions.

To better understand how financial, product and process enablers/disablers may relate to disruptions of the pharmaceutical supply chain, analysis was performed on a dataset developed from a number of FDA and other sources describing financial characteristics

of drug manufacturers and drug shortages. The remainder of this section describes the data, analytical methodology applied, results and implications on manufacturing quality and associated ratings.

Figure 10 Feedback Mechanism for Manufacturing Quality Investment and Supply Disruptions
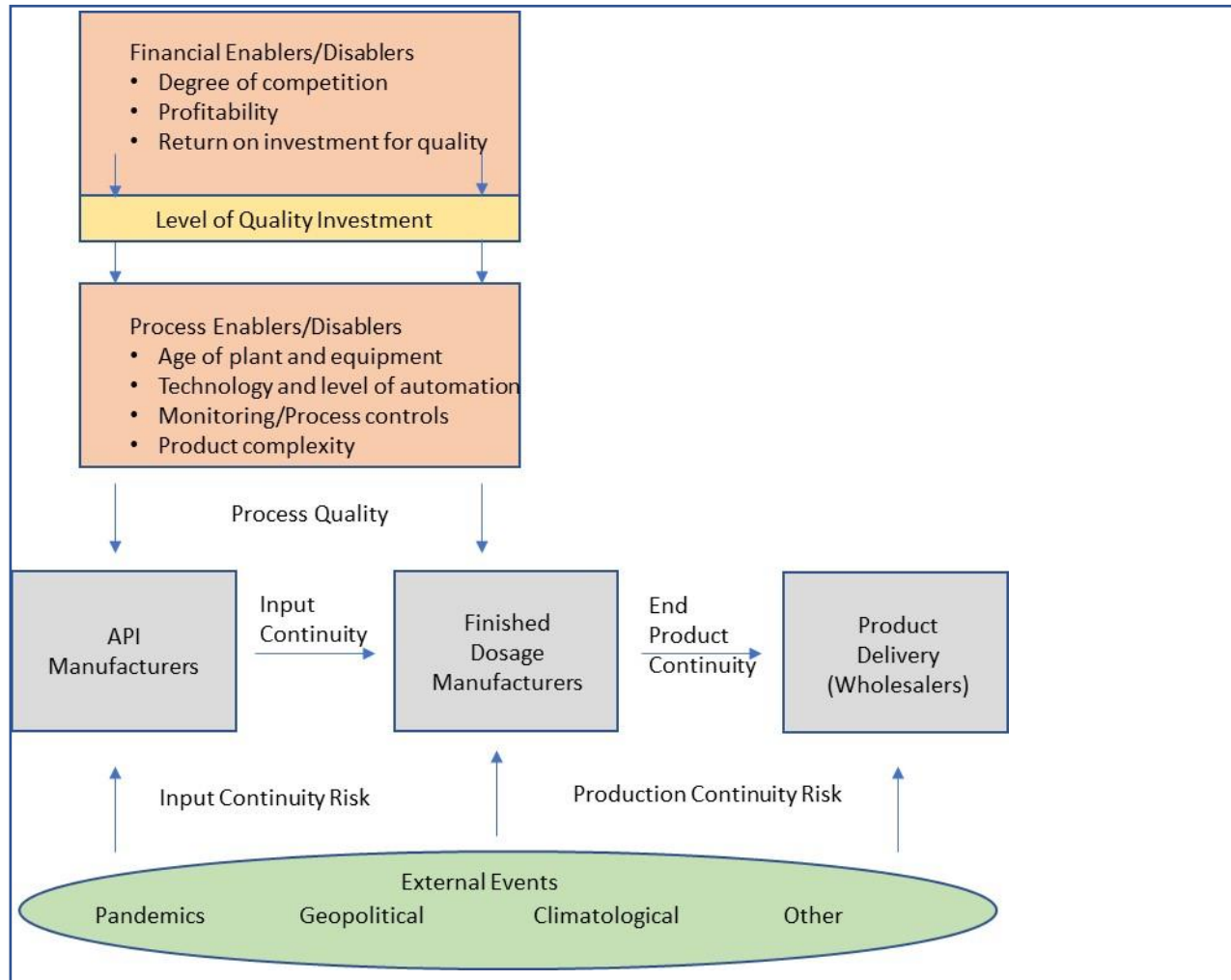
DRUG SHORTAGE DATA

The data used in this analysis were taken from several publicly available FDA and financial datasets and merged together resulting in a dataset describing key financial information on manufacturers, proxies of market competition, product characteristics, compliance information and data on drug shortages. The data sources and their relation

to this merged drug shortage data are depicted in Figure 11. Since the focus of the analysis was to understand how manufacturer financial profile, products, market competition and manufacturing quality affect drug shortages, three FDA datasets were incorporated into the final dataset for this analysis. The FDA's Drug Shortages data was one of these sources.[32] Key information in this data which spans the period 2012-2021 include the initial posting date for a shortage, the reason for the shortage, company name (manufacturer), product generic name, presentation, and therapeutic category. The duration of a drug shortage in number of days can be computed from this information which serves as the target variable of interest for a machine learning analysis described later in this section. The reason for drug shortage included such categories as issues in complying with CGMP standards, product discontinuation, increased product demand, shipping, manufacturing and regulatory delays, among some others. This drug shortage data served as the foundation for merging with the other data. The FDA Orange Book Data was used to create a variable used as a proxy of the degree of market competition for a drug product, i.e., the number of manufacturers as this data includes the applicant name.[33] Merging the Drug Shortage and Orange Book Data required creating a common field to merge on. Trade Name, Route of Administration, Active Ingredient, and Dosage Form fields from the FDA Orange Book data were merged in with the FDA Drug Shortage Generic Name field.[34] A text mining algorithm was used to associate the company names with the closest match possible among name strings. Since more than one applicant was found for a drug product in the Orange Book data, the number of manufacturers were aggregated to define a Number of Companies variable which represented a proxy of the degree of competition for a drug product. It should be noted that the applicant's name is not always the same as the actual manufacturer of the product as an applicant could engage with a CDMO or other company to produce the product. Another source of data used to refine the number of manufacturers variable was the FDA's eDRLS (electronic drug registration and listing system), a portion of which is publicly available.[35] Each registrant name was matched against the names in the drug shortage data to ensure as close a match to the company name as possible. The final FDA data incorporated into the merged dataset was on Warning Letters. A Warning Letter is sent to a manufacturer by the FDA upon a finding of some violation of FDA regulations such as a deficiency in manufacturing quality.[36] The number of Warning Letters received by a manufacturer were added up from this data and merged in with the other FDA data. This constructed

Figure 11 Drug Shortage Data Source Composition
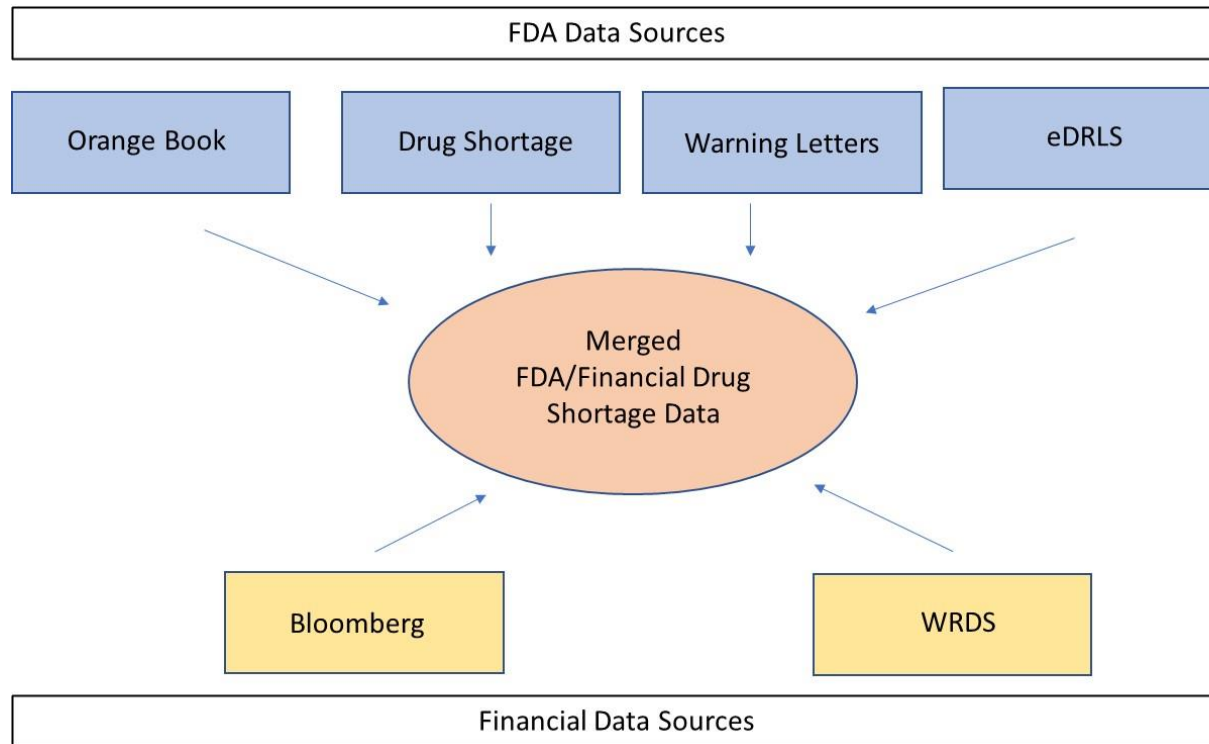
variable is used as a proxy of a company's manufacturing quality in the analysis. In theory, the larger the number of Warning Letters, the poorer the manufacturing quality of the firm may be.

The last two data sets used in the analysis provided financial information on publicly traded manufacturing companies.[37] Financial performance and operating data from Bloomberg and WRDS (Wharton Research Data Services) was merged in by company name from the FDA Drug Shortages data. Three specific variables were selected or computed from the data, total company revenues (dollars), profit margin (percent), and manufacturing costs as a percent of total operating expenses. These three variables were meant to reflect company size, financial performance and allocation of manufacturing costs. The data for each variable reflect the average of the three years leading up to and including the year of a specific drug shortage.

SUMMARY PROFILE OF DATA

From the FDA Drug Shortages Data, 434 observations were identified. Each observation reflects a specific drug product and company name combination. Within that data, 232

separate companies were identified. A total of 176 separate drug products in shortage were left after merging all FDA and financial database information and eliminating missing values on variables of interest in the analysis. A number of issues with the FDA data impose some limits on the analysis both in terms of sample size and variable definitions, however the final sample size was comparable with that used in the statistical analysis presented in the FDA Drug Shortage Report (163 drugs reported in shortage for that analysis). Some of these issues will be reviewed in the summary data analysis.

Figure 12 provides information on the magnitude and distribution of company financial performance variables used in the analysis. A quick takeaway from Figure 12 is that companies in the sample tend to be large and highly profitable. Average revenues and profit margin were $3.3 billion and 46 percent, respectively. Cost of Revenue (manufacturing costs) as a percent of total operating expenses averaged 60% for this group. On a univariate basis, no discernable pattern emerges in explaining the duration of a drug shortage.

From the FDA data a number of candidate variables of interest were created into categorical variables. A representation of these factors are shown in Figure 13. Route and

Figure 12 Characteristics of Company Financial Performance
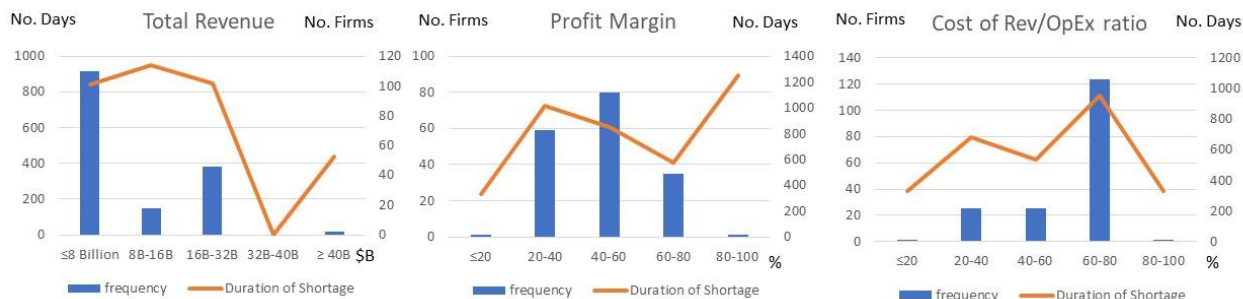
Dosage Form are included in the analysis to represent differences in drug products in terms of how they are administered and are classified into major types, e.g., epidural or oral for Route and capsule/tablet or injection for Dosage Form. The Therapeutic Category variable from the FDA Drug Shortages data was used to proxy manufacturing complexity. Several categories were defined, including analgesics, anesthesia, and oncology. The Reason variable is adapted from the Reason for Shortage variable in the FDA Drug Shortages data. This variable was included to determine if any relationship between the

Figure 13 Candidate Nonfinancial Variables for Drug Shortage Analysis
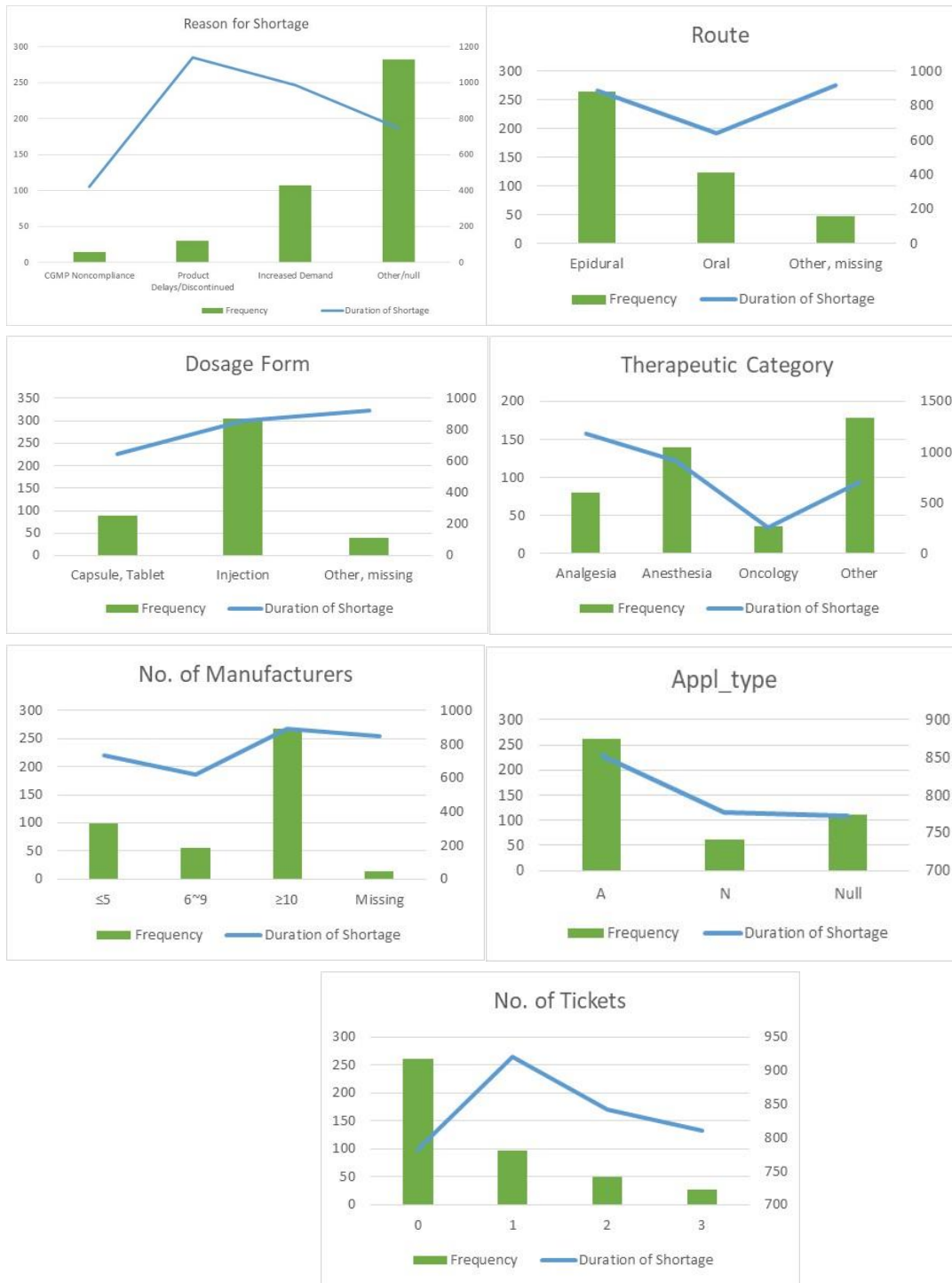
Note: Left-axis = Number of manufacturers, Right Axis = Number of Drug Shortage Days

duration of a drug shortage and issues with manufacturing process, demand or product discontinuation could be identified. There may be reporting issues with this data supplied by the manufacturer. Only 15 observations were attributed to a lack of compliance with good manufacturing practices. Since this data is unable to be validated it is possible that these numbers could be underrepresented in the sample. Other major categories of interest included Delays or Discontinued Product, and Increased Demand. Most observations were either not filled out or labelled Other. This information gap is potentially significant for drug shortage analysis and should be a major priority of the FDA to require manufacturers to report accurately and for the FDA to validate that data. There is ample precedent for such efforts from other federally regulated industries such as banking, where each quarter institutions are required to submit detailed information from their balance sheets and income statements. The data requirements for the FDA Drug Shortages data are far less than this and with some refinement and review by FDA could enhance future drug shortage analysis.

Another variable included in the analysis was whether the drug was a brand or generic product (Appl_type) based on the type of application, ANDA or NDA. Most of the sample in shortage were generics. The number of manufacturers for each drug product was used as a proxy of market competition. In this sample, the majority of drugs were produced by 10 or more companies. The last variable in the analysis was the number of Warning Letters (No. of Tickets) per manufacturer. While most manufacturers of drugs in shortage had no Warning Letters, forty percent had 1 or more Warning Letters.

A correlation analysis was performed on these variables and duration of drug shortage and the results are shown in Figure 14. The darker the color, the stronger the correlation with red shading of a cell signifying positive correlation and blue shading indicating negative correlation. While there appear to be a number of variable segments indicating a relatively strong correlation with each other, the correlations of candidate variables with the duration of a drug shortage variable of interest are relatively low or moderate. A more robust assessment of these factors is required, however, to draw any definitive conclusions.

MACHINE LEARNING ANALYSIS OF DRUG SHORTAGES

While a number of hypotheses can be formed with respect to each of the variables and the duration of a drug shortage, it is likely that a standard statistical regression analysis may be unable to identify key patterns in the data such as inherent nonlinearities and interaction effects between variables. As a result, a machine learning analysis, specifically XGBoost, or extreme gradient boosting for decision tree analysis is used. Boosting is a technique that builds on and improves results from earlier model iterations by creating updated models where the more recent model predictions are added back with previous model results to form an ensemble prediction.

As mentioned earlier in the summary analysis of the data, the target variable of interest to explain is the duration of a drug shortage. An XGBoost method is applied to the target variable and features (candidate variables) described earlier. Two models were developed; Model 1 uses the larger database of 434 observations that omits the financial variables. This model was run to check on the importance of the nonfinancial variables using a larger dataset. Model 2 uses the sample of 176 observations that includes the manufacturer financial variables. For both models, additional specifications were tested changing out Route and Dosage Form in the models based on the similarity of those factors. The final results are reported using versions of Models 1 and 2 that include Route based on model performance measures, although both versions show comparable performance. The overall R^2 of Model 1 and 2 were .82 and .83, respectively. To understand the effect of each variable (feature) on the duration of drug shortage, a SHAP, or SHapley Additive exPlanations value is produced. SHAP values quantify the overall marginal contribution of a feature to a model predicted outcome. SHAP is defined as the following:

$$19.\ SHAP_{feature}(x_i) = \sum_{s=1}^{S} \left(s * \binom{S}{s} \right)^{-1} \left[P_{s(i+j)}(x_i) - P_{s(j-i)}(x_i) \right]$$

where x_i represents feature i (e.g., total revenue), s is the set of combinations of features i and j with total number of features S, and P is the model prediction of that feature combination. A summary of the output from these models is found in Figures 15 and 16. Figure 15 displays each feature's average SHAP value contribution to the model with higher SHAP values indicating greater model impact of that feature. Features at the top of Figure 15 for both Models 1 and 2 exhibit the most importance to the model and those at the bottom the least importance. Based on this view, the manufacturing cost ratio,

increased product demand and 10 or more manufacturers are the top 3 model features in Model 1 followed closely by total company revenues. Much lower on Figure 15 is the reason for shortage from noncompliance with good manufacturing process feature. The other proxy of manufacturing quality, namely number of Warning Letters (No. of Tickets) also does not exhibit a strong contribution to model output. Looking at Model 2 results (without the financial variables and with a larger dataset), several therapeutic categories (Analgesia, Oncology and Anesthesia) wind up as dominant factors along with the >=10 manufacturers variable.

Figure 14 Correlation of Candidate Variables and Duration of Drug Shortage
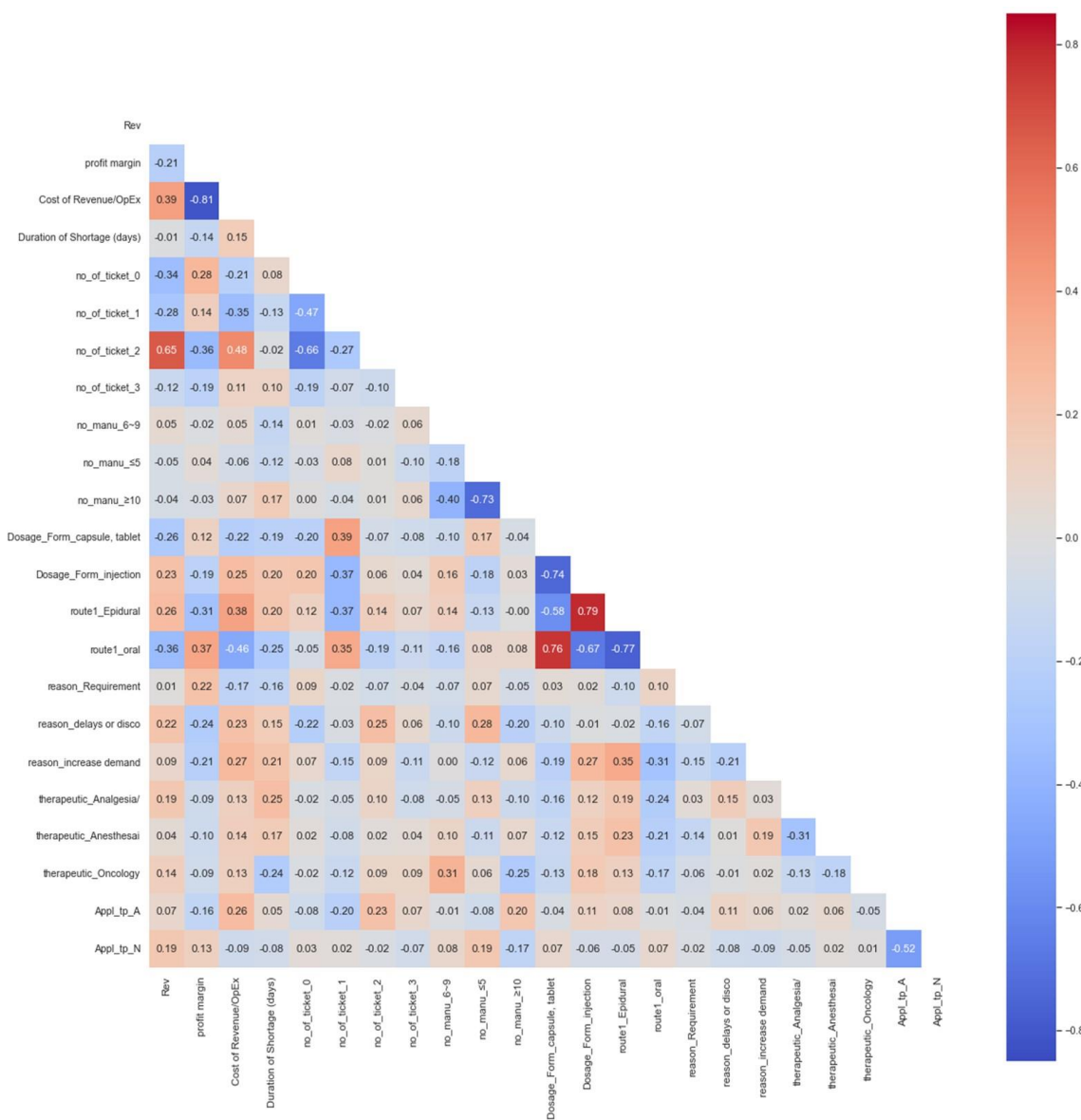
To obtain a more granular view of each feature's contribution to drug shortage duration, consider Figure 16 for Models 1 and 2. For each feature, every observation is plotted against the x-axis indicating its effect on the model. Observations where the value of the feature is large are depicted in red and low feature values are shaded in blue. Clustering of observations show up as clumps by feature. For example, most manufacturers with lower revenues appear to experience longer shortages, while the opposite is the case for manufacturers with higher revenues. In terms of the manufacturing cost ratio feature, again the observations tend to be bifurcated into groups where high ratios contribute to longer shortages as well as the opposite, so it is unclear that this feature is a reliable indicator of drug shortage duration. The pattern spread for each feature in Figure 16 indicates the dispersion of a feature's model contribution. Injection dosage form, for example for Model 1 has a relatively wide dispersion where a number of observations indicate both a low and high contribution to the model output.

Figure 15 Feature Importance to Explaining Drug Shortage Duration
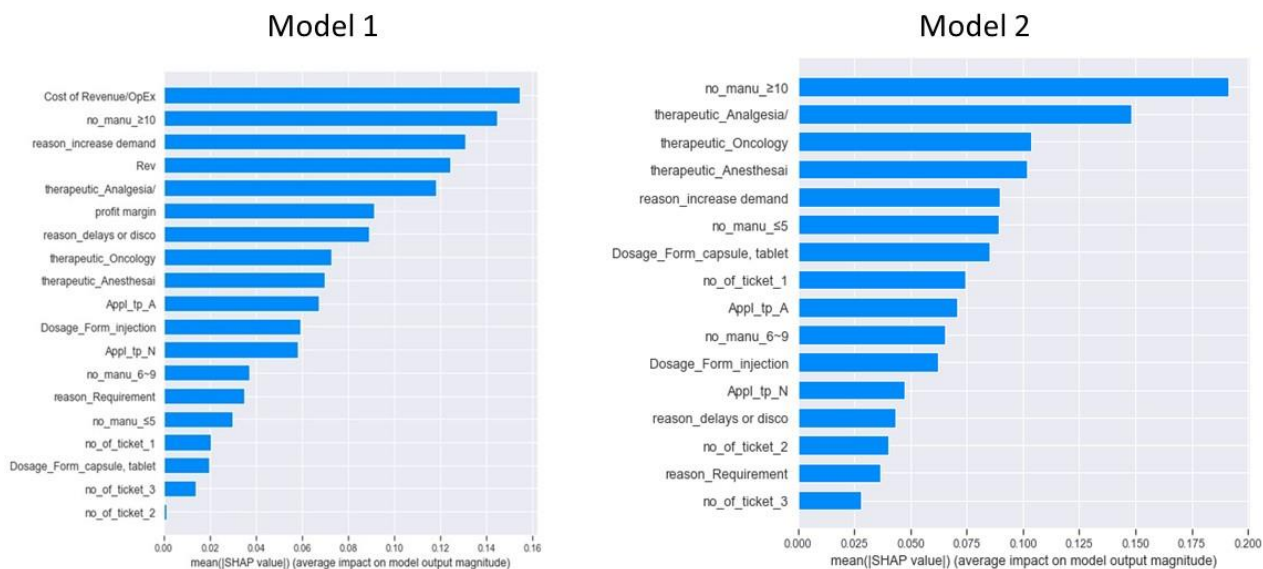
Another way to gain a sense of the effect of possible interactions among variables is to plot feature values by the SHAP value for that feature. Figure 17 provides a depiction of that for the manufacturing cost ratio feature in the analysis which has the largest overall contribution to the model. As mentioned above, the direction of the effect of this ratio is not clear and the model contribution could be impacted by other features along with manufacturing cost ratio. This can be seen from Figure 17 by the dispersion across values

Figure 16 Feature Importance Distribution and Duration of Drug Shortage Model Impact
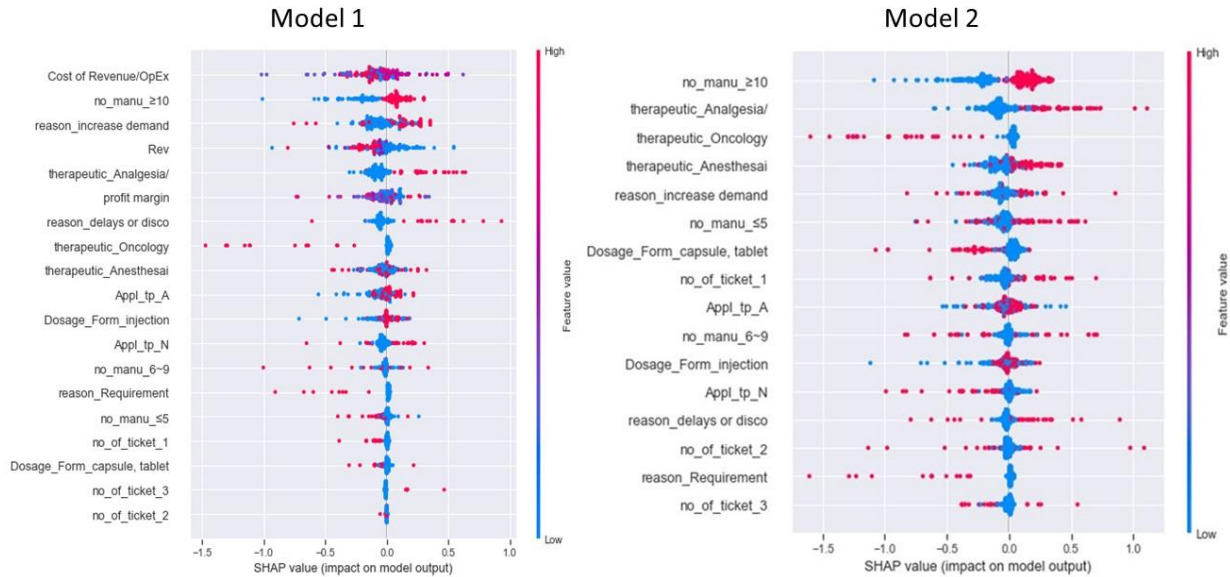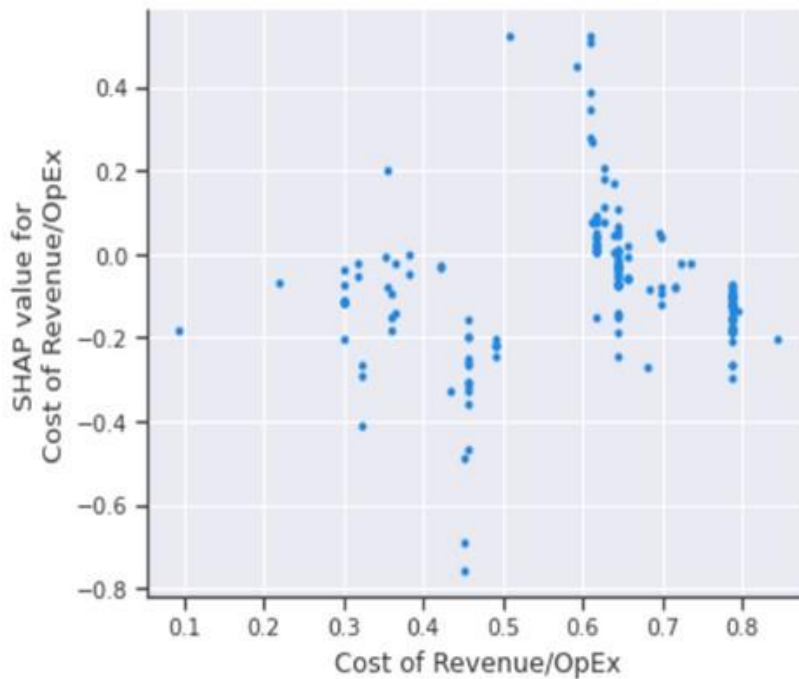

Figure 17 SHAP Values for Manufacturing Cost Ratio

of the feature (i.e., ratios) in terms of just this feature's SHAP value. For example, for ratios around 60% or so, there is a wide dispersion in this feature's SHAP value which indicates the potential of other features to be affecting the importance of manufacturing cost ratio to the model. Examining such relationships may shed additional light on such effects and await future analysis and improvements in the available data.

The results from this analysis provide an incomplete picture of the impact of financial performance, operational costs and other nonfinancial factors contribution to explaining the duration of drug shortages. There does appear to be some evidence that smaller companies (based on revenue) may be associated with longer drug shortages. Manufacturing cost ratio did not appear to be a major driver in extending or shortening a drug shortage though for a number of companies lower profit margins appear to be associated with longer drug shortages. There was some evidence that the manufacturing quality proxy variables, reason for shortage due to compliance issues with good manufacturing quality practices and number of Warning Letters contributed to explaining drug shortages, however the strength of those factors was not large compared to other factors. Other factors such as increased demand and 5 or fewer manufacturers for a drug product tended to be more important and indicated a longer drug shortage duration.

Drug shortages are multifaceted and that seems to be consistent with the results from the machine learning analysis. Market and business factors such as product demand, manufacturing concentration, company size and profit margin appear to have more of an impact on explaining the duration of drug shortages than proxies of manufacturing quality, despite these variables showing that they have important contributions to the model. The publicly available data on manufacturing quality may not be as robust as internal FDA and so further analysis of that data might yield a more definitive conclusion.

A SURVEY OF QUALITY RATINGS USE CASES

Previous sections have highlighted a number of issues associated with implementation of a quality rating system for pharmaceutical manufacturing by the FDA. These issues are critical to the long-term viability and effectiveness of such a rating process. Understanding experiences from adjacent or different industries in using quality ratings can provide insights and lessons that can enhance the success of the QMM program.

Toward that effort 5 quality use cases from different industries have been identified for detailed examination. Quality ratings are used extensively in industry and government for a variety of reasons. Automotive and aerospace companies have for years leveraged the use of quality ratings for suppliers and other manufacturing applications. Financial services, food, and chemical industries are other examples where variations of quality or risk assessment tools and ratings are used in elevating consumer awareness to product quality and health, financial viability and manufacturing quality.

The five issues of interest in this section where use cases can shed additional light on the viability of quality ratings are the following:

1. Experiences from existing quality ratings programs at FDA. Focusing on the FDA's Center for Devices and Radiological Health (CDRH) Case for Quality Program and associated Voluntary Medical Device Manufacturing and Product Quality Pilot Program and extensions serves as a basis for identifying lessons from the program that could be applied to QMM in terms of implementation, participation, participant concerns, barriers and solutions.

2. The issue of asymmetric information and product quality is an important theme cited in an earlier section that can be addressed by the introduction of a quality rating system. To investigate this further, a review of the used car market before and after advances in information technology provided car buyers with data on a car's history is conducted. Such services as CARFAX® provide consumers with access to information on used cars that can help them in negotiating the purchase of a used vehicle.

3. Another issue examined in this study is the impact of a quality rating on pharmaceutical pricing. Although the market is characterized by relatively inelastic demand, the economic models and numerical analyses reviewed suggest that there is some potential for quality-based adjustments to price and/or rebates to occur if quality ratings are adopted by the industry. A review of quality ratings used by the Centers for Medicare and Medicaid Services (CMS) to assess nursing homes provides insights into this issue. There is some evidence that ratings applied in this instance have led to pricing differentials for nursing homes based on quality.

4. Successful long-term viability of the QMM Program in part depends on industry adoption. An examination of characteristics of early- versus late- adopters of voluntary ratings for ISO-14001 environmental management standards (EMS)

among manufacturing firms is conducted to better understand the differentiators in a company's participation in such activities. In addition, a review of how other regulatory policies in the chemical industry affect voluntary participation in EMS and Responsible Care standards provides insight into how a QMM voluntary quality rating system might be affected by other standards such as CGMP.

5. The implementation of quality ratings by a federal regulatory agency on companies adds another dimension to understanding their use and application in terms of market reaction, and nature of regulatory oversight in light of differential ratings results between companies and other issues. To understand the experiences from another highly regulated industry's federal regulator using a rating process, the bank CAMELS ratings process used by federal safety and soundness regulators is studied.

USE CASE 1: FDA CDRH CASE FOR QUALITY PROGRAM

In 2011, CDRH initiated its Case for Quality program after reviewing data on manufacturing quality issues of medical devices over the years. This analysis discovered several impediments to improvements in medical device manufacturing quality including a lack of engagement among the manufacturing industry on quality initiatives, industry focus on compliance rather than quality, and a lack of data and analysis on quality to incent manufacturers to invest in quality processes and activities.[38] The CDRH review concluded that attention and investment in manufacturing quality can lead to lower costs and regulatory risk for companies that ultimately translate into better products for patients and consumers. The QMM Program and CDRH Case for Quality share a number of features.

The Case for Quality program features a two-pronged approach; focus on quality and stakeholder engagement.[39] The focus on quality sees compliance with FDA standards for manufacturing as a minimum practice and companies should strive to establish a range of "critical-to-quality" practices that go well beyond baseline standards. This includes attention on a number of design and production activities to better monitor and test for manufacturing process issues and defects proactively. Stakeholder engagement is considered essential in terms of the medical device industry's acceptance of CDRH's case for quality initiatives. CDRH engages with a variety of industry stakeholders including

the Medical Device Innovation Consortium which draws from the manufacturing, healthcare and device buyer community, among others.

In 2018, the CDRH launched its Voluntary Manufacturing and Product Quality Pilot Program. The Pilot leveraged the Capability Maturity Model Integration (CMMI) approach to rating quality of medical device manufacturers. A subset of the 25 practice areas identified in the CMMI methodology were used in the Pilot assessment process. According to the MDIC report, the Pilot was highly successful on several levels. Industry experience was favorable, with 80% of participants viewing the assessment as value-added to enhancing quality for firms and most participants viewed it as a positive experience.

Several issues were identified following the Pilot that required corrective action. One issue identified was the assessment cost. The program required all participants to absorb the costs of the appraisal which created a heavier burden on smaller manufacturers. Some adjustment to cost was made for smaller firms by the CMMI and larger companies provided some staff to augment the appraisal process as a way of further addressing cost issues for smaller participants. Industry interest in the pilot during the first year and a half from its start appeared strong, moving from about 15 manufacturers at the pilot's inception to 46 a year and a half later.[40] Moreover, it was reported that the 1-year retention rate of participating companies was over 80 percent. One issue common between the CDRH and QMM pilot programs is availability of FDA resources going forward to broaden the program. Resource constraints to implement ratings on a wider scale appear to be a major limiting factor of widespread industry adoption that in turn reduces the effectiveness of the ratings process overall.

From all appearances, the CDRH pilot has been successful in bringing attention to quality processes in the medical device industry. Criteria for its success were FDA's willingness to cultivate interest with industry and other external constituent relationships by championing quality, sharing important data and creating transparency for pilot participants. As the industry regulator, obtaining buy-in from manufacturers for such a program requires establishing a level of trust and fairness without fear of retribution that quality ratings would be used as a regulatory stick and not a carrot in practice. Identification and clear communication of what risk-based regulatory flexibility can be

granted, if any, by rating could be an important incentive to attract more manufacturers to participate in such programs. Promotion of proactive measures by industry to engage in quality investment and self-identification of problems and reporting to FDA is an ideal state in a regulatory environment. The CDRH program appears to have navigated these issues successfully thus far.

USE CASE 2: ASYMMETRIC INFORMATION IN USED CAR MARKET AND ACCESS TO PRODUCT QUALITY INFORMATION

In 1984, CARFAX® was founded in part to address odometer tampering in the used car market. Since then, CARFAX® has become a major force in providing detailed information regarding a vehicle's history that had previously been unavailable to buyers. By tapping into a wide variety of data sources, the company has been able to revolutionize the used car buying experience for consumers by reducing information asymmetries that had disadvantaged buyers. As presented in an earlier section, Akerlof's lemons problem and quality uncertainty for used cars highlighted the market imperfections created when one side of the market, in this case buyers are at an information disadvantage from the other (sellers). Pricing in such a market it was argued forces good quality used cars from the market as the price for used cars regardless of quality is set at an average level as buyers are unable to distinguish vehicles on the basis of quality.

CARFAX® filled this void by collecting a wide variety of data on a used car's history. The company leverages data from state motor vehicle agencies on vehicle registrations, stolen car records, accident reports, lien information and the like as well as from insurance companies, collision service and auto repair establishments, among others. This data can help identify issues associated with vehicle mileage (i.e., odometer fraud), accidents, or whether the car was damaged in some natural disaster such as a flood. These types of events can create widespread risk to potential used car buyers in their aftermath. For example, following Hurricane Harvey in 2017, it was estimated that 150,000 cars in Texas were damaged from flooding.[41] CARFAX® is clear in disclosing that the company does not have complete information on all cars, so some information asymmetry still exists in the market. While a CARFAX® report does not provide a numeric rating for a vehicle per se, it does provide buyers using their service with an estimate of a car's value based on service or damage history or other factors captured by CARFAX®. Taking such a risk-

based approach to valuation, buyers are better informed on what to offer sellers in the negotiation process.

The cost of gathering information on a used car's history would be a significant deterrent to individual buyers. The ability of CARFAX® to systematically gather this information on an ongoing basis, incorporate it in a consistent manner and provide easy access to reports for customers are features that have enabled this business to grow over time. Importantly, CARFAX® reports are not used just by buyers, but sellers find value in having reports on their vehicles as a way to boost interest in a vehicle and to obtain better pricing as well.

The implications of the CARFAX® experience for the QMM Program are that introduction of ratings to a market can reduce information asymmetry that leads to various market imperfections.[42] Note that in the case of CARFAX®, a report is not a mechanism to directly promote quality improvements in the used car market. Some dealers might preemptively take action, however, to address a vehicle defect before its sale if a CARFAX® report surfaces an issue that requires repair before it goes on the market. CARFAX® is not a sole provider of car history reports and so finds itself in competition with other providers such as AutoCheck. These services are voluntarily procured by buyers and sellers for a fee and the growth in the use of these reports indicates that the market values this type of information. The widespread use of such reports and quality-based value estimators in the used car market provides a reality check that quality ratings reduce information asymmetry, potentially leading to improvement in market pricing for quality differentiated products.

USE CASE 3: IMPACT OF QUALITY RATINGS ON NURSING HOME PRICING

In 2008, CMS introduced its 5-star nursing home rating system for consumers, Nursing Home Compare. The rating is comprised of the following components; health inspections, staffing and facility quality. A composite score for a facility's health inspection results and complaints in the past 3 years is also developed and serves as the basis for establishing the overall nursing home score.[43] These ratings are publicly available at the CMS Care Compare website and provide consumers with an ability to

generate lists of nursing homes within a specified range and compare these companies based on certain features in addition to ratings.[44]

Nursing care is a significant expense for elderly or infirm patients, costing between $94,000-$108,000 per year for an individual.[45] While Medicaid, when available, covers a significant portion of these costs for patients, it does not cover all costs and many individuals without Medicaid (private pay) are forced to pay for skilled nursing care on their own. Consumers require information on the cost and quality of services provided by these entities given the number of available providers.

As described in the CARFAX® use case, ratings can reduce information asymmetry problems and market imperfections. One question that arises, however, is whether and to what degree a quality rating can affect the price of a good or service. Beyond the issue of price elasticity which was reviewed earlier for pharmaceutical products, understanding the relationship between ratings and price in the CMS program can provide insights into how a QMM rating system might affect manufacturing quality. Pharmaceutical manufacturers have at least three motivations for pursuing a quality rating. First, if increasing quality reduces costs, or improves product pricing, a manufacturer would be economically incented to make quality improvements. Second, from a market standpoint, if a higher rating meant landing on a preferred supplier tier where access to manufacturing other products was possible that would incent a manufacturer to invest in quality. A third motivating factor would be potential regulatory relief or flexibility for having a higher rating. Some empirical research has investigated the relationship between quality ratings for nursing home care and pricing which helps understand the first of these factors that might incent improvements in quality.

Huang and Hirth hypothesized that the CMS nursing home rating system would reduce information asymmetry and result in quality-differentiated pricing based on consumer willingness to pay.[46] It was further believed that a quality rating system would have asymmetric impacts on pricing for high- and low-quality facilities. High quality nursing homes were expected to have larger price increases than lower-rated facilities. Of some significance to pharmaceutical markets, the authors hypothesize that price increases would be more pronounced for higher rated nursing home in more competitive markets. Where scarcity exists for high quality care units due in part to regulatory requirements

for nursing home care, higher-rated facilities may be able to raise prices more than their lower-rated counterparts. The parallel to the pharmaceutical industry would be to hypothesize that capacity constraints in competitive markets in the presence of a widely adopted QMM rating may boost prices for high-rated manufacturers more than for lower-rated ones.

Using data on nursing homes for 2008-2009, Huang and Hirth estimated a statistical model predicting nursing home prices as a function of quality ratings. In addition to each facility's 5-star rating, the model controlled for a number of other factors including facility characteristics (e.g., number of beds), patient characteristics (e.g., race and gender composition), county level market concentration effects, income and age. State dummy variables and Medicaid reimbursement rates were also included in the statistical analysis.

Among the findings from the analysis was that prices for the highest rated nursing homes rose 4.8-6.0 percent more than the lowest rated facilities following implementation of the rating system. Moreover, much of the higher prices observed were found to be in relatively competitive markets, corroborating the hypotheses and the results were found to be statistically significant. While the research did not investigate the effect of price elasticity in the nursing home market, there is some evidence that the market is less inelastic than for pharmaceuticals.[47] That might imply smaller price increases for a market with less price elasticity such as pharmaceuticals. Importantly, the study's authors also noted that there could be some negative welfare implications for nursing home consumers at high-rated facilities due to higher prices paid. This could potentially have parallels to consumers of pharmaceutical products if manufacturing quality ratings were implemented widely across the industry, however, price inelasticity and other factors would be expected to limit such effects.

USE CASE 4: CHARACTERISTICS EARLY AND LATE RATINGS ADOPTERS AND THE EFFECTS OF REGULATORY DIFFUSION

A critical consideration for the success of a voluntary rating system is industry adoption. The issue of early- and late- adopters has been well-researched across other industries and some of the findings of this work have implications for a QMM rating system. Notwithstanding issues with resource capacity by FDA to build out an industry-wide program, to have maximum impact, such a rating system in the end state should have

broad reach in pharmaceutical manufacturing. Understanding what distinguishes early- from late-adopters of industry standards or ratings could help guide the FDA in expanding the number of participants in the QMM ratings process post-pilot.

Of some interest here are studies of manufacturing company adoption of voluntary environmental management systems (EMS) as embodied in ISO 14001 certification. ISO 14001 establishes a framework for how companies can develop processes and policies to improve their environmental performance. Early versions of the standard appeared in the late 1990s and today approximately 360,000 companies are certified.[48] Such success in a voluntary program begs the question of what drives some firms to invest in such programs earlier than others?

In a study of French manufacturing firms, Ozusaglam et al., investigated the characteristics of early- and late- adopters of ISO 14001.[49] Factors cited as motivations for early adoption of EMS include economic, market, public opinion, regulatory, firm characteristics and prior experience with other voluntary standards such as ISO 9001 for quality management. The authors were particularly interested in understanding what firm-specific features are likely to result in early adoption of ISO 14001. The study's authors sought to empirically test 6 hypotheses regarding voluntary adoption of ISO 14001. Companies more likely to adopt ISO 14001 early were hypothesized as being larger firms and those with multiple operating units based upon their access to more financial and nonfinancial resources; companies with prior experience implementing total quality management (TQM) standards; companies with an international presence and more technological complexity, and finally, companies with high productivity levels.

Ozusaglam et al., estimated two Probit binary choice statistical models to explain differences between early-, late- and non-adopters. A number of firm characteristics were included as explanatory factors such as firm size, operating structure, international presence, adoption of ISO 9001 or TQM standards, manufacturing type (e.g., high-tech), among others. They confirmed their hypotheses that larger firms with experience adopting ISO 9001 or TQM were more likely to be early adopters of ISO 14001. Early adopters were also more likely to be international in scope and operated in moderate to high-tech manufacturing industries and their results were stronger in one of their samples that was oriented more toward innovative firms. Another important finding was

that adoption, regardless of the timing by a company resulted in productivity gains presumably via cost savings associated with improvements in production processes.

These findings have crossover implications for pharmaceutical manufacturing and voluntary QMM ratings. FDA could "grow" participation in their rating process strategically by developing an outreach plan targeting pharmaceutical companies that have features similar to those of early adopters of ISO 14001. Some of those firms may have participated in the pilots, however, increasing their ranks could help build visibility and momentum among industry participants. Once early adopters begin to communicate their experience and results externally, other nonparticipating manufacturers may find their way to volunteering for the rating program. From there a "bandwagon" effect could take hold as it has done in the case of ISO 14001 certification.

USE CASE 5: FEDERAL REGULATORY AGENCY DEVELOPMENT OF RATINGS FOR US DEPOSITORY INSTITUTIONS

For decades, federal safety and soundness regulators of regulated US depository institutions (i.e., commercial banks, thrifts and credit unions) have used a 1-5 rating system, the Uniform Financial Institutions Rating System (UFIRS) to determine the strength of an institution's financial condition and operations. In a sense, the UFIRS, otherwise known as CAMELS ratings is a type of institution quality rating where quality is defined by financial performance and risk. For nationally-chartered commercial banks, the Office of the Comptroller of the Currency oversees their safety and soundness which includes periodic onsite examinations of banks. In addition, each quarter banks are required to submit detailed information about their balance sheets and income statements that are publicly disclosed. This information, along with other data collected by the OCC and from examinations form the basis for developing a bank CAMELS rating.

CAMELS ratings are not publicly disclosed but are made available to bank management and their boards. Moreover, the rating process is not statistically-based, but determined by a set of specific criteria:[50]

C – Capital adequacy
A – Asset quality
M – Management

E – Earnings

L – Liquidity

S – Sensitivity to market risk

Each component is rated on a 1-5 scale, with 1 being the highest, or best rating and 5 the worst, or lowest. A composite score is developed from all of the components identified above. CAMELS ratings are periodically updated by the regulator. Beyond providing a systematic way of evaluating banking institutions, the ratings find their way into how the OCC (in the case of national banks) and other bank regulators (e.g., the FDIC) incent a risk-based approach to bank management.

A CAMELS rating has significant implications for a bank's operating plans. Banks, for example that are not sufficiently capitalized, which would be reflected in the "C" component of CAMELS, may be restricted from growing their asset base, required to suspend dividends, required to seek approval for mergers and acquisitions, among other restrictions. In addition, CAMELS are used to determine a bank's FDIC deposit premiums. Banks with better CAMELS ratings would enjoy lower premiums, reflecting their lower risk to the bank insurance system.

The implementation of a ratings process for regulated commercial banks has been moderately successful over the years in containing risk in the banking system, however, it has been far from perfect. In the years leading up to the 2008 financial crisis, for example, the regulator for the thrift industry at the time, the Office of Thrift Supervision was found to have been slow to update the CAMELS rating for Washington Mutual, the largest thrift at the time with more than $300 billion in assets that ultimately was put into receivership by the FDIC in 2008 due to excessive risk-taking and deficient loan manufacturing processes.[51]

The experience of federal bank regulators with industry ratings has implications for the FDA and its QMM ratings program. It illustrates how a mandatory rating process can be used to influence company behavior. In this case, since CAMELS ratings are mandatory, the impact is industry-wide. The ratings process in this example is tied to a set of policies that provide direct financial incentives to strengthen bank internal processes and capabilities. Since the QMM ratings program is voluntary, developing specific policies

that provide regulatory incentives to rating participants would help expand adoption of the program for FDA.

Importantly, the data requirements imposed on regulated banks are far more significant than those for pharmaceutical manufacturers. The banking industry has become accustomed to providing that information over the years and it has been invaluable to the regulatory agencies for developing policies and oversight strategies for the industry. One area for further consideration is for FDA to enhance data requirements for all pharmaceutical manufacturers with respect to their operations, risk management capabilities and financial resources dedicated to quality management. Likewise significant strengthening of requirements on drug shortage data and associated reports should be considered.

SUMMARY AND CONCLUSIONS

Ensuring that pharmaceutical manufacturers not only adhere to current good manufacturing process but go beyond to embrace a culture of quality has far-reaching consequences for the industry, the health care community and consumers. A focus on quality has over decades and across many sectors of the economy demonstrated direct economic benefits accruing to firms adopting quality management best practices including greater operational efficiency, lower costs, and greater productivity. These financial benefits have been empirically established.

The pharmaceutical industry is one of those industries that is critical to the welfare and health of society and as a result is highly regulated. The proliferation of drug products over the years, the globalization of the pharmaceutical market, increasing complexity of drug products, manufacturing processes, and supply chains warrant attention by both the FDA and the industry. Continued drug shortages in this country are startling and concerning both to policymakers and also consumers and patients dependent on uninterrupted access to high quality drug products. The FDA's safe and effective doctrine assures the American public that drug products consumed in this country meet a high standard of quality. However, disruptions in the supply chain over the years in part have been attributed to deficiencies in manufacturing practices that could be addressed with a mature quality management program. Empirical analysis of the duration of drug shortages in this study, for example identified firm size, market concentration, allocation

of operating resources to manufacturing and demand as major drivers explaining the duration of a shortage.

A set of 5 research questions were of interest in this study to better understand factors critical to the effectiveness of the QMM rating program. This included an assessment of the industry's market structure, economic incentives to invest in quality manufacturing processes, and risks and limitations to implementation of a rating program.

The structure of pharmaceutical markets is varied and complex. Multiple touchpoints on the demand and supply-side of the market introduce various risks. On the supply-side, supply chains are complicated and in many cases market pressures and other characteristics limit input and end product diversification. Some drug products are susceptible to API shortages for a variety of reasons and bifurcation in the market for finished dosage form product between brand and generic drugs, for example, likewise can affect the degree of competition and product diversification in a market. The market is characterized by a large number of sellers, many of which are quite large and can exert considerable market power in product negotiations.

On the demand-side, multiple participants such as consumers, health plan sponsors, and drug purchasing intermediaries such as GPOs and PBMs impact how the effects of a drug shortage are transmitted in the market, prices paid for products and their demand. The critical nature of pharmaceuticals for end users explains why prices are relatively inelastic. The confluence of these characteristics in supply and demand, the presence of federal pharmaceutical programs for some markets (Medicaid, Medicare and VA, for example) portray a market that does not fit nice and neatly into one economic model from which to explain market behavior with and without a quality rating system.

The current state of the pharmaceutical market is characterized by an asymmetric information problem that introduces a number of market imperfections as a result. FDA's safe and effective doctrine has effectively provided consumers and other demand-side participants with comfort that the drug products used are all of a high minimum standard of quality. However, below the surface, differences among manufacturers exist in terms of their adoption of best practices in quality management. This has significant implications for the likelihood of a drug shortage over time for companies unwilling or

unable to go beyond CGMP standards. Absent a standardized methodology to assess this differential in manufacturing quality, the market is unable to differentiate drug products on the basis of manufacturing quality. Costs imposed on pharmacies and healthcare providers during a drug shortage are not built into price negotiations directly.

A quality rating was demonstrated in multiple economic models and numerical analyses to allow for drug product differentiation which could affect equilibrium outcomes compared with markets lacking a quality rating system. Notwithstanding inherent price inelasticity in these markets, some degree of price differentiation could be realized as a mechanism for incenting investment in manufacturing quality. A more likely incentive to come out of a quality rating system would be to use ratings in drug formulary tiering. Manufacturers have economic incentives to have their products placed high on product tiering systems and so this might be a strategy for buying organizations to pursue.

Looking at other industries, the viability of a quality rating system for the pharmaceutical industry seems bright. Ample precedent for ratings systems exists demonstrating their utility in incenting investment in quality from an examination of several use cases. FDA's CDRH has experienced solid success and momentum in their implementation of voluntary assessments of medical devices. The CMS nursing home rating system, for example, was found to have facilitated significant price differentials between high and low-rated nursing homes. The introduction of car history reports by CARFAX® has revolutionized the user car market by arming consumers with detailed information on potential damage and defects for a used auto.

Long-run, the success of the QMM rating program will depend on several factors to widen participation among manufacturers. Making QMM ratings mandatory for API and FDF manufacturers would certainly achieve full industry participation, comparable to what bank regulatory agencies require of depository institutions with regard to their CAMELS ratings. Following this path has obvious tradeoffs for the FDA, industry and consumers but would be a way to realize full adherence to QMM practices. The costs to implementing this would clearly need to be weighed against the benefits.

A more pragmatic solution is to continue to evolve the QMM voluntary pilot programs into a broader program of voluntary adoption. There is evidence from other markets that

with sufficient time and resources, what starts as a limited voluntary program can blossom into a widely adopted program. This was described in the use case for early- vs late- adopters of ISO 14001. The FDA could target certain manufacturers found in other studies to be likely to adopt a quality management process. And by linking a quality rating to differential regulatory requirements and flexibility, the FDA would not only be able to provide more efficient risk-based regulatory oversight, but also incent greater participation in this program. Ultimately, a transparent, standardized manufacturing quality rating, by way of a combination of economic and regulatory incentives has the potential for promoting investment in manufacturing quality practices and thereby lessen the potential for disruptions and risks in the pharmaceutical supply chain.

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