

US Generic Pharmaceutical Industry Economic Instability

Understanding drivers of economic uncertainty
in the US generic pharmaceutical industry
and its implications on supply instability

April 21st, 2023

Anthony Sardella¹

Washington University
Olin School of Business
Center for Analytics and Business Insights

Anthony Sardella
Senior Research Advisor
Center for Analytics and Business Insights
& Adjunct Lecturer, Olin Business School
Washington University in St. Louis
sardella@wustl.edu

¹for whom correspondence should be directed.

Introduction

Over the past decade, many US generic companies operating in the US have shuttered operations or are operating with significant idle capacity¹. Economic conditions indicate that this environment will worsen, increasing quality and supply risks to the nation's healthcare and security.

COVID-19 created a significant demand shock to the US drug supply chain revealing the United States' significant reliance on foreign production of essential drug active pharmaceutical ingredients. The FDA's Center for Drug Evaluation and Research (CDER) shared that as of August 2019, 72% of FDA-approved API manufacturing facilities were outside of the US. A recent 2021 deeper dive revealed that approximately 75% of COVID-19 related drugs, 97% of antibiotics, 92% of antivirals, and 83% of the top 100 generic drugs consumed have no US-based source of APIs. Even common over-the-counter products are dependent on overseas producers, for instance, 80% of the global supply of PAP, a precursor material for acetaminophen, is only available from China. Notably, COVID-19 highlighted this operational and geopolitical vulnerability as 44 pharmaceutical companies were rendered inoperable in China and the government of India ceased the export of 26 medicines, including acetaminophen and antibiotics, by rule.

A confluence of factors leads to many of the most essential medicines being among those most in shortage. As medicines, particularly high-volume essential medicines, become generic, market entrants and competition increases, market pricing decreases, profit margins erode, lower cost production options are explored, and a transition occurs to the least-cost locations to gain economy of scale. Over time, price and margin erosion lead to essential medicines becoming low-margin commodities, and eventual production and supply issues create vulnerability to shortages and susceptibility to low reinvestment, a cycle we term "The Commoditization Loop." The FDA's analysis of Drug Shortages, published in 2019 and updated in 2020, highlighted three root causes of shortages: low profitability, low value for quality, and complex, global supply chains. All three causes are prevalent in essential medicine production.

Our research focuses on an analysis of pricing and earnings trends of the generic industry as a driver of vulnerabilities in the supply chain. It includes an analysis of Average Manufacturer's Price (AMP) from the Medicaid.gov database over the past six years. Secondly, we analyzed public earnings data on the top twenty-four generic companies by revenue over the past five years. We combine the findings with an analysis of the Return on Invested Capital for the similar top twenty-four generic drug companies for the past ten years. Lastly, we analyzed the trend in addressing FDA manufacturer warning letters. A discussion is included on how such trends provide an indicator of an economically unhealthy US industry sector. Considerations for addressing resulting risks to the sustainability and resiliency of the US generic drug supply chain are provided.

The US Generic Pharmaceutical Market

The US generic pharmaceutical market plays a significant role in the healthcare of the nation. Generic manufacturers – whether operating domestically or abroad – account for over 90% of the US marketplace's prescriptions². By rule, these products are commodity products as they must be perfectly substitutable to the

¹ Sardella, 2022. U.S. Generic Pharmaceutical Manufacturer Available Capacity Research Survey. Washington University Olin School of Business. Center for Analytics and Business Insights

² Gupta et al., 2019

FDA, "2021 Annual Report" Office of Generic Drugs, page ii; <https://www.fda.gov/media/156066/download>

originator (i.e., branded) product, and to each other.³ Because they are interchangeable, price becomes the dominant factor in market success and these medicines are, generally, inexpensive. The US generic pharmaceutical market is designed to be hyper-competitive driven by several unique industry dynamics.

Competition on the Dimension of Price

Four key considerations for successful commercialization of a product, referred to as the marketing mix, include the product itself, pricing, promotion, and place (i.e., distribution). With no distinguishing product differentiation or quality tracking in the industry to distinguish product quality differences, market competition in the generic drug industry, without market exclusivity, focuses on the dimension of price. Competition on price has overall proven effective in reducing the costs of medicines. A recent FDA report highlights that within the first year of a generic approval, “prices fall by more than 75% compared to the brand price⁴,” with many products achieving greater than 95% price reductions as additional competitors appear⁵. This cost reduction allows for a reduction of healthcare costs, with benefits distributed across stakeholders.

Price Erosion and Consolidation

Price erosion can be defined as a negative price realization in the market. The perceived value of a product declines over time during the lifecycle of a product as a result of attempts at competitive matching that accelerate pricing and margin erosion.

Many factors contribute to price erosion, including shorter product lifecycles, budget constraints, and increasingly sophisticated buyers. The number of generic pharmaceutical manufacturers serving the US market has risen 50% since 2014⁶. Manufacturers are vying for the business of fewer buyers – three buying groups make 92% of the wholesale generic purchases in the US⁷. Consolidation has accelerated that price-based competition, with frequent bidding cycles used to lower the price for a given generic⁸. The bidding cycles require manufacturers to update supply price reduction within a matter of weeks upon the request of the wholesalers. The wholesalers are then free to move volume to the lowest bidder at the end of the cycle. While the bidding cycles ensure supply at the best market price, it also results in no long-term guarantee or certainty of demand for manufacturers despite significant capital investments. Industry interviews with generic companies as part of this research indicate that it is not uncommon for a generics drug supplier to have their entire business up for bid through the course of a calendar year creating significant risk in the financials of the business. These cost reduction trends continue year after year, in what has been referred to as the ‘race to the bottom,’ squeezing generic manufacturer’s margins further and further degrading the economic viability of the manufacturing supply base.

³ FDA, “Facts About Generic Drugs”; <https://www.fda.gov/media/83670/download>

⁴ FDA, “Estimating Cost Savings from New Generic Drug Approvals in 2018,2019, and 2020” CDER, page 4; <https://www.fda.gov/media/161540/download>

⁵ FDA, “Generic Competition and Drug Prices” CDER, page 2; <https://www.fda.gov/media/133509/download>

⁶ IBIS, “Generic Pharmaceutical Manufacturing in the US” [Generic Pharmaceutical Manufacturing in the US - Number of Businesses | IBISWorld](#)

⁷ AAM, “AAM calls out threat of consolidation among purchasers” 2022; [AAM Calls Out Threat Of Consolidation Among Purchasers :: Generics Bulletin \(informa.com\)](#)

⁸ Ibid

An analysis of Average Manufacturer's Price (AMP) from Medicaid.gov database⁹ provides insight into understanding industry price erosion trends over the past six years.

Industry Average Manufacturing Price Trend Analysis

An analysis of the Average Manufacturing Price trends over the past six years indicates a decrease of 47% from an average of \$3.15 to \$1.47 for the high-volume generics consumed over the period. Top generics are defined by most units dispensed per METYS/Symphony US market prescription data. The same set of generics were analyzed to control the impact of new generic launches and changes in mix and volume. Figure 1 illustrates the six-year trend.

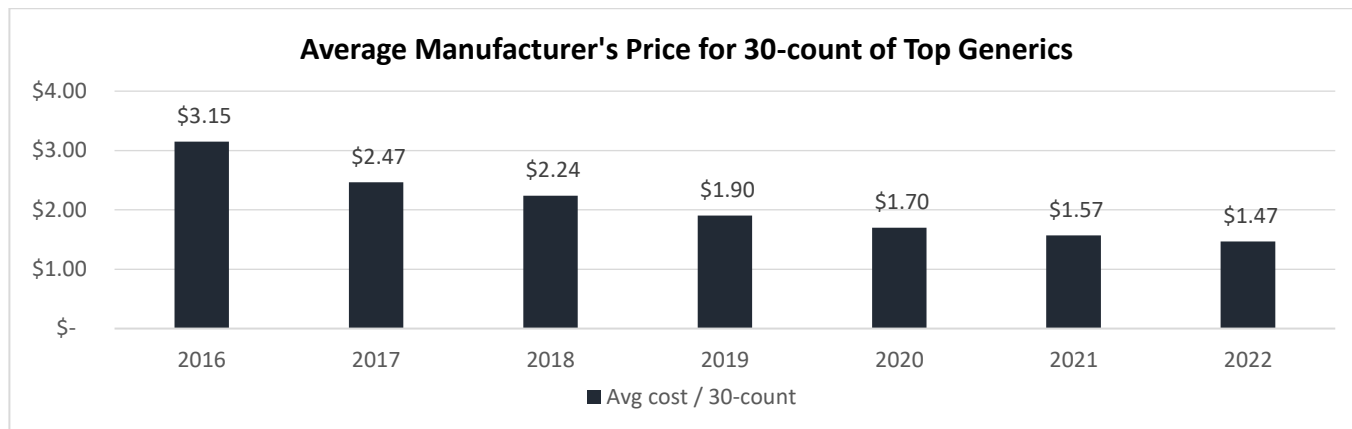


Figure 1. Average Manufacturer's Price for 30-count of Top Generics.

Offshoring of US Drug Manufacturing Supply

Partly in response to these pricing pressures, low-cost manufacturing locations have replaced the US as the predominant source of medicines. Supported by government subsidies, lower costs of labor, and less regulatory oversight, manufacturing has shifted over twenty years.

The aforementioned persistent cycle of price erosion has led to a continued decline in US active pharmaceutical ingredients (API) manufacturing facilities over the past five-year period. In a study of the geography of prescription pharmaceuticals supplied to the USA¹⁰ Shivdasani, et. al., reported a decline from 125 facilities in 2014 to 103 in 2019 representing an 18% reduction in available US API manufacturing facilities.

Today, the majority of common generic medicines have no US source of active pharmaceutical ingredient (API), the component of the medicine providing therapeutic benefit. Some recent studies have highlighted the current situation:

⁹ <https://www.medicaid.gov/medicaid/prescription-drugs/medicaid-drug-rebate-program/medicaid-drug-rebate-program-data/index.html>

¹⁰ Shivdasani, et. al., 2021. The Geography of Prescription Pharmaceuticals Supplied to the USA: Levels, Trends, and Implications. Journal of Law and the Biosciences. Jan-Jun.

- Greater than 80% of APIs for FDA-defined essential medicines and over 90% of top antibiotics and antivirals have no US manufacturing source¹¹
- Less than 5% of large-scale API sites, globally, are located in the US – the majority of large-scale manufacturing sites are in India and China¹²
- India and China have the greatest number of API facilities supplying the US market and over ten percent of these facilities have an FDA Warning Letter¹³

The ‘race to the bottom’ on pricing has moved sources of supply further from the US market, creating logistical and political risks in the pharmaceutical supply chain. Over the past three years, the magnitude of geo-political risk has been highlighted with the Government of India cutting of exports of 26 pharmaceutical products whilst navigating the early stages of COVID¹⁴ and a leading Economist in China highlighting the threat China can use in limiting exports of antibiotics¹⁵. The reliance on China is compounded by Indian API manufacturing reliance for 80% or more of chemical starting materials from China, something that the Government of India has prioritized addressing through their Production Linked Incentive (PLI) scheme¹⁶.

Company Earnings Trend Analysis

Predictably, hyper-competition has had a direct effect on manufacturer’s earnings as competitive forces challenge even amongst the low-cost country manufacturers that are leading providers of medicines to the US market. We analyzed public earnings data on the top twenty-four generic companies by revenue over the past five years to understand the state of industry earnings and trends. Figure Two illustrates a comparison of EBITDA to Revenue, a measure of operating profitability, for the twenty-four leading publicly traded generic manufacturers (many of which primarily operate in low-cost countries) over the past five years. A rapid degradation in earnings has occurred over the last quarters due to these price pressures.

All top manufacturers saw a degradation in earnings since mid-2021, but the bottom quartile has notably fallen below a 15% EBITDA to Revenue ratio. The implications of such economic indicators can be dire: reduced earnings will lead to cost-cutting and a reduced ability to invest in new product development, factory maintenance, overheads, technology innovation and investment in quality systems.

¹¹ Sardella, Anthony. “The US Active Pharmaceutical Ingredient Infrastructure”, Aug 2021; CABI Olin Business School at Washington University

¹² IBID

¹³ Socal, Mariana et. al. “Competition and Vulnerabilities in the Global Supply Chain for US Generic Active Pharmaceutical Ingredients” HealthAffairs.Org; 2023

¹⁴ Ellis-Petersen, Hannah, “India limits exports after supplies hit by coronavirus”, Mar 2020; The Guardian; <https://www.theguardian.com/world/2020/mar/04/india-limits-medicine-exports-coronavirus-paracetamol-antibiotics>

¹⁵ Palmer, Doug “US Policymakers worry about China ‘weaponizing’ drug exports”, Dec 2019; South China Morning Post; <https://www.politico.com/news/2019/12/20/policymakers-worry-china-drug-exports-088126>

¹⁶ Khan, Shariq, “Budget 2023: Pharmacy of the world has Chinese Achilles heel” Jan 2023, The Economic Times; <https://economictimes.indiatimes.com/small-biz/sme-sector/budget-2023-pharmacy-of-the-world-has-a-chinese-achilles-heel/articleshow/97046291.cms>

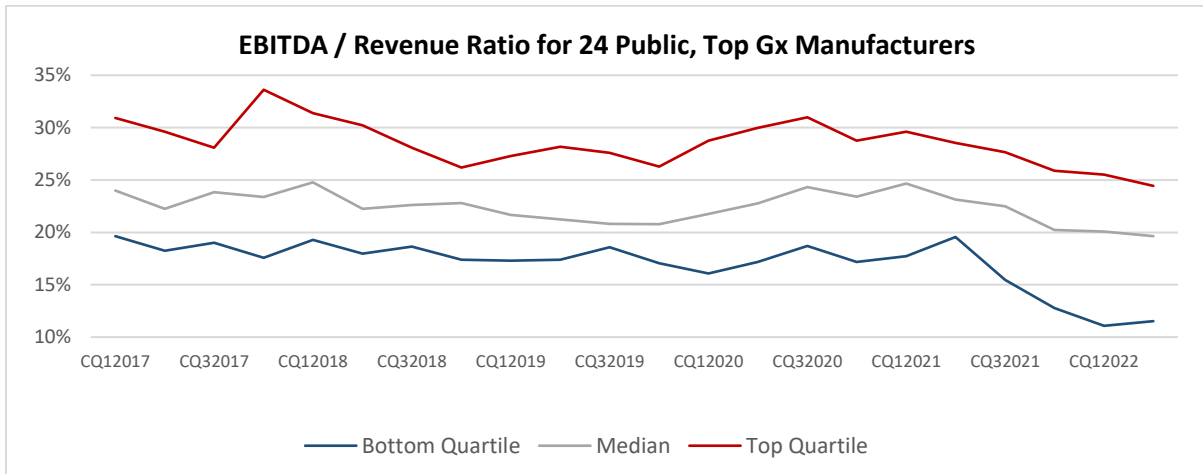


Figure 2. EBITDA to Revenue for leading US Gx market manufacturers: Ajanta, Amneal, ANI, Aurobindo, Bausch, Cipla, Dr. Reddy's, Endo, Gland, Glenmark, Granules, Hikma, Jubilant, Lannett, Lupin, Mayne, Perrigo, Sun, Strides, Taro, Torrent, Viatrix, Wockhardt, Zydus

Further analysis of the Return on Invested Capital (ROIC) for the leading twenty-four generic manufacturers over the past ten years is illustrated in Figure 3. Data from S&P's Capital IQ was analyzed to determine the Return on Invested Capital which provides a measure of the health of a sector in its ability to obtain a strong return on the capital investments made. The generics industry maintains a low and degraded rate of return on deployed capital with a median industry ROIC of only slightly above 5% in 2022. The recent inflationary period, globally, shows that investments into some generic companies are likely to offer negative return for owners and investors, further challenging the ability of these manufacturers to sustain their enterprises.

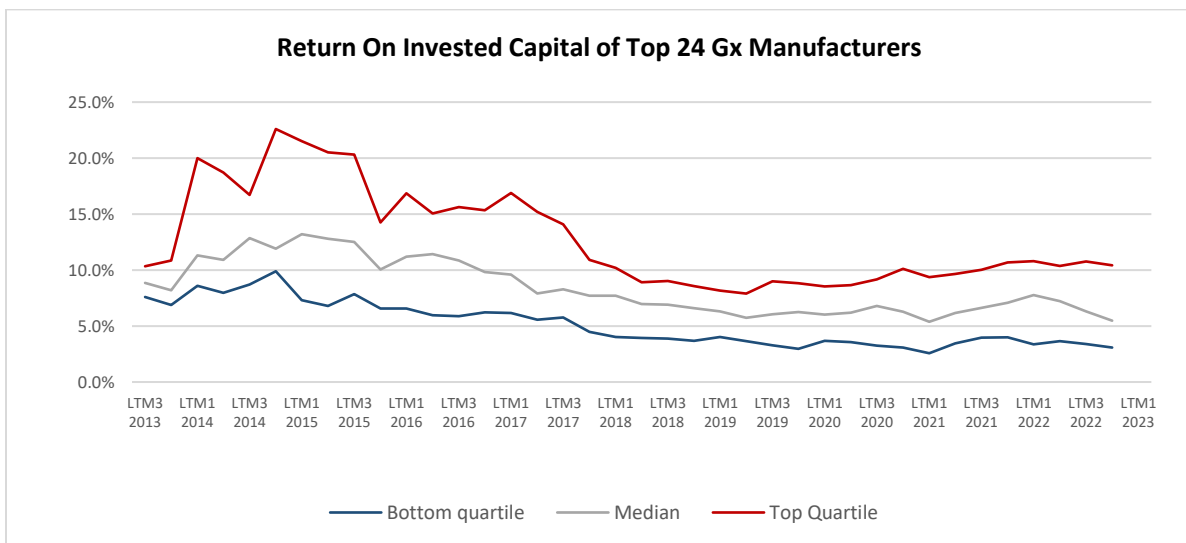


Figure 3. Return on Capital for leading US Gx market manufacturers: Ajanta, Amneal, ANI, Aurobindo, Bausch, Cipla, Dr. Reddy's, Endo, Gland, Glenmark, Granules, Hikma, Jubilant, Lannett, Lupin, Mayne, Perrigo, Sun, Strides, Taro, Torrent, Viatrix, Wockhardt, Zydus.

Low return on capital invested is highly problematic given the high costs of commercializing a new generic drug. A study completed by the Eastern Research Group in 2021 on behalf of the US Department of Health and Human Services, Office of the Assistant Secretary of Planning and Evaluation assessed the costs of generic drug development and approval assessment. The research developed an analytical framework for examining the expected net present value (NPV) to a generic developer in a spectrum of sized drug markets. It revealed an estimated \$6.5M average cost of capital for the simplest case. With uncertainty created by the bidding process post the exclusivity period, many medicines have negative estimated net present values driving a lack of investment in production and availability of medicines. In particular, essential medicines with low margins become unattractive, creating greater threat of shortages.¹⁷

Quality and Compliance Challenges

Lastly, we analyzed the trend in addressing FDA manufacturer warning letters. The drop in overall EBITDA to Revenue ratio since 2018, correlates to a reduction in the ability for manufacturers to address sometime expensive and complex compliance challenges. Figure 4 illustrates an analysis of the FDA warning letters database¹⁸ for the past five years. A similar number of warning letters has been issued annually ranging from a low of 113 in 2018 and a high of 284 in 2020. However, the rate of industry close-out of regulatory issues (i.e., issues resolved to the FDA’s standards) has dropped from one-in-four warning letters closed out to one-in-twenty by 2022.

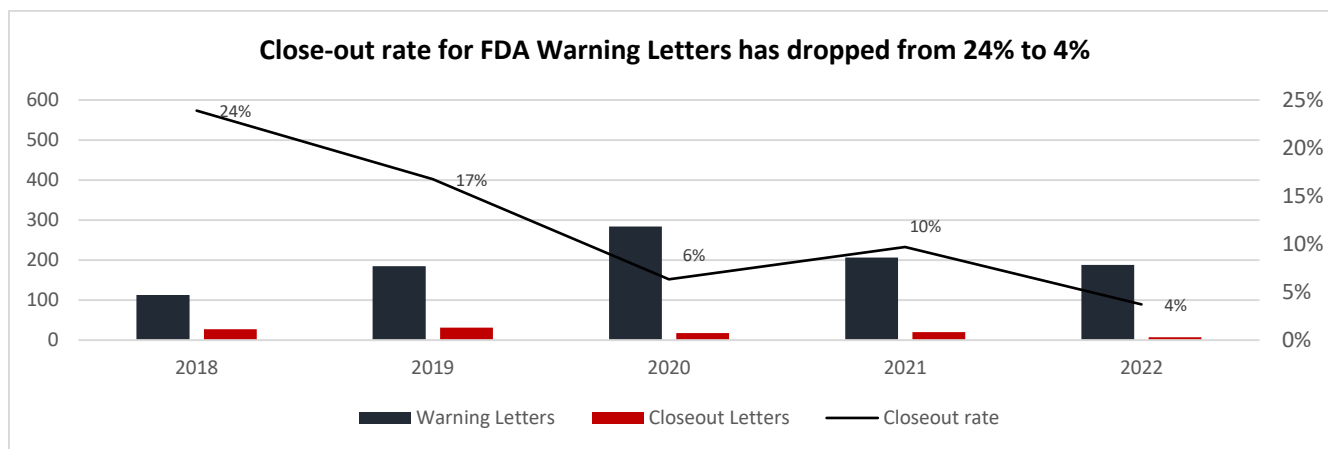


Figure 4. FDA Warning Letters issued versus closed out, FDA Database: all CDER, CBER, Division & Office of Pharmaceutical Quality, Division & Office of Biological Quality, and Office of Manufacturing Quality (excludes veterinary and food activities)

The magnitude of these quality and compliance issues is significant with 26% of the nation’s prescriptions now being supplied by companies that have received warning letters since 2020 (Figure 5). That figure rises to 50% of all prescriptions supplied by companies with FDA warning letters when we look back to 2015. It is important to note that these manufacturing sites do not fully meet FDA manufacturing standards and thus the warning letter to

¹⁷ Department of Health and Human Services, Administration for Strategic Preparedness and Resilience (ASPR). Essential Medicine Fact Sheet. [Essential Medicines Fact Sheet \(hhs.gov\)](https://www.hhs.gov/essential-medicines)

¹⁸ <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters>

take corrective action. However, it does not necessarily indicate an issue regarding the safety of the drug product, it indicates a non-conformance to manufacturing standards.

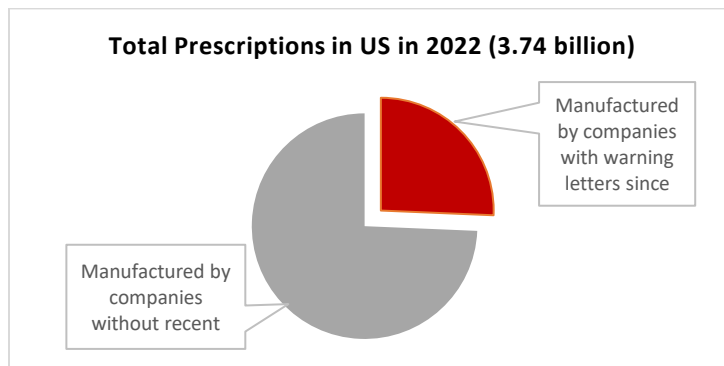


Figure 5: Proportion of nation's prescriptions filled by non-compliant manufacturers

Industry interviews as part of our research as to causes of the decrease in close out letters indicated one of the drivers for this decreasing trend of closing out compliance issues is the high cost to address compliance and quality challenges relative to the low profitability.

In 2022 alone, multi-national manufacturers closed facilities in New Jersey, Illinois, California, and Missouri. Each were closed after receiving repeat FDA observations of non-compliance and/or warning letters. Ultimately, these facilities, which were being operated by foreign ownership, concluded it was more economical to cease manufacturing in their US based sites or use alternative sites than to fix the compliance issues.

Considerations for Addressing Economic Viability of the US Generic Pharmaceutical Drug Supply Chain.

The economic viability of the industry supply of generic medicines which represents 90% of prescriptions for American's is diminishing – an assessment of the landscape indicates an ongoing economic degradation based on current market and non-market externalities. Delays in addressing these risks can lead to negative implications for the US healthcare system. There are multiple potential options for consideration to address these weaknesses, but they each must acknowledge and combat the economic root causes.

We offer considerations for addressing the drivers of economic lack of viability based on the data findings and on industry interviews.

(1) Addressing the quality-price trade-off using a transparent quality score.

A driver of The Commoditization Loop for generic drugs is the inability to differentiate on product quality which is a dimension of market competition in virtually all other industries.

A recent article in the Journal of Pharmaceutical Innovation highlights the deeply seated challenges in addressing the quality risks¹⁹. The authors propose building on the FDA's 2015 guidance for proposed quality metrics and supporting a decentralized screening network of testing facilities to objectively

¹⁹ Almeter, P.J., Isaacs, J.T., Hunter, A.N. et al. FDA Approaches in Monitoring Drug Quality, Forces Impacting the Drug Quality, and Recent Alternative Strategies to Assess Quality in the US Drug Supply. J Pharm Innov 17, 269–282 (2022). <https://doi.org/10.1007/s12247-022-09659-5>

evaluate product quality. A combination of self-reported and objectively verified quality metrics can provide awareness to stakeholders of any potential risks.

Expanding on this proposed model in a manner common across other market sectors, we propose providing this information through a publicly available quality score to inform buyers – both individual consumers and the network of wholesalers, payors, and providers in the industry. While quality can be a complex construct, adopting common industry manufacturing quality standards for conformance to specifications, and analysis of variation from standards such as occurs in industries such as the automotive industry, would enable opportunities for competition on the dimension of quality.

Moreover, leveraging the US regulatory and purchasing power can tip the scales in favor of high quality and domestic manufacturers. Actions such as creating a monitoring system for finished drug quality performance, aligned with the FDA inspection data and publishing quality ratings could have a significant impact in establishing product differentiation, as shown through company quality performance, as a driver of market competition. Furthermore, supporting labelling guidelines that mandate country of final manufacturing and country of origin for active ingredients would also drive visibility of supply chain sourcing and introduce new variables for competitive differentiation. Such efforts would provide greater transparency on quality and compliance and can enable wholesalers, retailers, and consumers to make informed strategic decisions, which could reshape the marketplace away from purely a price-driven exercise.

(2) Countering hyper-competition through private-public public benefit entities.

Companies across the US healthcare landscape feel the challenges in the current model that lead to shortages, lower service levels and earnings.

To support local manufacturers amidst the COVID crisis, India launched a production-linked incentive (PLI) program and is using government funding to support expanding low-cost production of starting materials to wean the nation's reliance off China, their historic rival²⁰. Similarly, the US has invested in individual companies with mixed results given the complexity and opaqueness of supply chains. One company receiving millions in federal funding seeking to produce a US-sourced product remains reliant on imported APIs²¹. Based on the complexity of the problem – economically, politically, technologically – these company-specific investments will be very challenged to make a difference in the landscape of over 2,500 medicines in the US market. It will require a new innovative industry supply model to enable the complexities to be overcome.

One model being undertaken by the State of Missouri is to provide multi-year State investment and funding of a private-public partnership consortia, the API Innovation Center in St. Louis, Missouri. Located in the innovation district of Cortex, the API Innovation Center is a non-profit that has brought together partners across the pharmaceutical 'ecosystem': technology innovators, incumbent manufacturers, care organizations, and state and federal agencies²². The collective efforts on one such 'ecosystem' is targeted to create a domestic manufacturing base for an oncology product, Lomustine, to combat shortages and risks within a glioblastoma-treating product. The intent of this collaboration is to introduce new

²⁰ Government of India PLI Scheme homepage: <https://pharmaceuticals.gov.in/schemes/production-linked-incentive-pli-scheme-promotion-domestic-manufacturing-critical-key>

²¹ Rowland, Christopher "Trump backed start-up to make drug ingredients on US soil. It's new products rely on foreign suppliers"; Washington Post March 10, 2022

²² API Innovation Center @ Cortex; www.apicenter.org

technology, leverage existing infrastructure and align the economics for all parties to reward a high quality, resilient approach to pharmaceutical manufacturing. Such non-profit public-private efforts, where partner companies seek market-based solutions to problems, with State Government support demonstrate a high probability to address the level of supply chain risk being seen today. These collaborations aim to address pockets of poor supply chain performance, but scaling up to make an impact as the industry struggles will require attacking the market-place forces that create the ‘race to the bottom’ at their root.

(3) Overcoming market-place hurdles by de-risking industry investments.

The newly empowered ASPR Industrial Base Management and Supply Chain (IBx) effort focusing on existing manufacturers with proven quality track-records, can be a tremendous vehicle to address industry’s upfront capital investment challenges for US facilities. Leveraging existing idle manufacturing base can expedite stabilizing drug supply chains and save millions in spending. Funds that can be directed to the research and development into novel advanced manufacturing technologies that reduce the cost of production, improve the quality of product, worker safety of operations, and environmental footprint of such manufacturing. In one recent piece of work, an incumbent manufacturer estimated a 60% savings in capital and a 2–3 year acceleration if existing facilities are used to support domestic production efforts versus starting from a greenfield plot.

Government agencies increased funding support for industry coalitions that present the fastest, most efficient solutions to generic supply chain challenges also increases the probability of success by aligning incentives to bring these products to market prior to industry investments on development.

Lastly, the largest share of total health spending in the United States is born by the federal government (34%). However, the United States is unique in not having sourcing policies that favor and incentivize domestic manufacturing or manufacturers with stronger compliance records – a practice already employed in Germany, Brazil, India, and China. For example, improving provider reimbursements for US-made generic products and realigning preferred drug lists/formularies for Medicaid/Medicare is a policy change that can be undertaken by the federal government to enable an incentive for US based manufacturing. In the case of Medicaid, state governments can dictate similar adjustments (albeit with federal approval), presumably without the need for any additional legislative authority.



Anthony Sardella is Adjunct Professor at Olin Business School at Washington University in St. Louis. His research focuses on issues at the intersection of business, government, and society. He is also Senior Research Advisor at the Center for Analytics and Business Insights at the Olin Business School.

Disclosures: Author is member of the Board of the API Innovation Center, a non-profit dedicated to de-risking the adoption of advanced manufacturing technology to strengthen the domestic manufacturing of generic APIs.