07 May 2025

BY ELECTRONIC SUBMISSION: http://www.regulations.gov

Mr. Eric Longnecker
Deputy Assistant Secretary for Technology Security
Bureau of Industry and Security
U.S. Department of Commerce
14th St and Constitution Avenue, NW
Washington D.C. 20230

Re: Docket No. XRIN 0694-XC120 Pharmaceuticals 232 Notice

Dear Mr. Longnecker,

Civica, Inc. (Civica Rx) is pleased to make the following submission in response to the Bureau of Industry and Security request for comments on XRIN 0694-XC120 Pharmaceuticals 232 Notice.

About Civica

Civica is a non-profit sterile generic drug manufacturer established by U.S. health systems and philanthropies to reduce chronic drug shortages and ensure a safe and stable supply of essential medicines to U.S. patients. Civica's mission is to serve patients by making quality medications available and affordable.

In its six years of existence, Civica has delivered more than 218 million vials of 80 different sterile injectable generic medicines to 1400 member hospitals in 50 states. Civica drugs are chosen by U.S. health systems because they are products that are frequently in shortage or at high risk of future shortages.

In selecting suppliers, Civica prefers finished drug product and active pharmaceutical ingredient (API) from U.S. sources. Following that, we choose products from the E.U., Canada, or other jurisdictions with robust pharmaceutical regulatory oversight. We also source from carefully selected suppliers in other parts of the world, but we do not source from China unless the API is available nowhere else. In all cases, Civica conducts direct quality oversight of its suppliers, including in-person quality audits of facilities and regular ongoing quality reviews.

Along with contracting for Civica-labeled drug from existing Abbreviated New Drug Application[1] (ANDA) holders, Civica is developing its own ANDA submissions and recently completed construction of a state-of-the-art sterile injectable drug fill-finish manufacturing facility in Petersburg, Virginia. This facility was established with private funds and substantial federal support through ASPR/BARDA. Civica has several dozen ANDA medicines in development for this facility.

Civica's supply model is designed to mitigate the risk of drug shortages and support U.S. national security of domestically made generic medicines. Along with the quality oversight mentioned above, Civica enters multi-year, guaranteed minimum volume contracts with its hospital members and with its suppliers. This supply approach brings stability to the market; predictable volume also allows Civica to hold a reserve inventory, targeted at 6 months' supply of every medication. This adds further resilience to the supply chain, as it buffers supply disruptions in the market. This model has been shown to be more reliable and less costly than the traditional wholesale model for generic drugs.[2]

There is a strong inverse correlation between the price of a drug and its risk of being in shortage. Because Civica focuses entirely on preventing and mitigating drug shortages, the products we supply tend to fall at the low-end of the price range for generic sterile injectable medications – generally less than $2.40 per vial. This makes them particularly susceptible to competition from low-cost imported products from countries such as India and China.

The essential medicines supply chain

Generic drugs account for about 90 percent of all medications used in the United States. Demand is likely to increase in proportion to population growth and aging.

For at least 14 years, the generic medicines supply chain in the United States has been characterized by persistent shortages of essential medicines. At any given moment, there are typically hundreds of products on the shortage list maintained by the American Society of Health-

[1] An Abbreviated New Drug Application is the process by which the U.S. Food and Drug Administration approves a generic drug.

[2] Dredge C, Scholtes S. "Vaccinating Health Care Supply Chains Against Market Failure: The Case of Civica Rx." NEJM Catal Innov Care Deliv 2023;4(10). DOI: 10.1056/CAT.23.0167

System Pharmacists.[3] Shortages occur across therapeutic categories of generic drugs, including antibiotics, local and general anesthetics, neuromuscular blockers, sedatives, opioids, blood thinners, reversal agents, pressors and more. Drug shortages raise health care costs and can have serious consequences for patients, including delayed care and potential medication errors. Sterile injectable products are predominantly affected, though not exclusively, due to the complexity of manufacturing and the low profit margins associated with these products.

When considering the resiliency of the medicines supply chain, it is important to recognize that chronic drug shortages have now become a built-in outcome of the current system. The immediate cause of most shortages of sterile injectable drugs is quality problems in the manufacture of the finished dosage form. But it is widely acknowledged that the root cause is the low cost of these products, which reduces the incentive or ability for manufacturers to invest in quality or in newer manufacturing facilities and pushes production offshore to low-wage markets with less sophisticated regulatory oversight, where quality problems proliferate, and the FDA presence is less consistent.[4] (Indeed, more than half of shortages occur in products that cost $1 per unit or less.[5])

Today, about 42 percent of the U.S. market, by volume, for sterile injectable drug products is produced in this country, followed by India (22 percent), China (14 percent), and the E.U. (13 percent).[6] For active pharmaceutical ingredient (API), a widely cited figure is that 80 percent of supply comes from outside the United States, predominantly India, China and Europe. Upstream of API are the precursor ingredients, or key starting materials, which also come mostly from outside the United States.[7]

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[3] American Society of Health System Pharmacists. Current drug shortage bulletins. https://www.ashp.org/drug-shortages/current-shortages/drug-shortages-list?page=CurrentShortages&loginreturnUrl=SSOCheckOnly

[4] For example, see FDA "Drug Shortages: Root Causes and Potential Solutions," 2019; Brookings "Federal Policies to Address Persistent Generic Drug Shortages," 2023; Duke Margolis, "Advancing Federal Coordination to Address Drug Shortages" 2023.

[5] IQVIA Inst. for Hum. Data Sci., *Drug Shortages in the U.S. 2023: A Closer Look at Volume and Price Dynamics*, (Nov. 2023), *available at* from www.iqviainstitute.org .

[6] United State Pharmacopeia. Medicines Supply Map. 2024 data (personal communication). Excludes large volume parenterals, such as 1-L saline bags.

[7] The economics of KSMs are beyond the scope of this comment letter, but an analysis by Derek Lowe, a pharmaceutical chemist and longtime industry commentator, provides useful insights: https://www.science.org/content/blog-post/pharmaceutical-tariffs-what-and-how

For certain categories of drugs, there is little U.S. production capacity. These include antibiotics, such as the generic penicillin- and cephalosporin-class drugs that account for about two-thirds of inpatient antibiotic use. Other categories with extensive reliance on overseas production include cytotoxic drugs used in cancer treatment and blood thinners such as heparin that are derived from porcine mucosa.

The principal factor driving the off-shoring of the generic drug supply chain is the pursuit by purchasers of the lowest possible costs, which is incentivized by current reimbursement policies and consolidated purchasing by Group Purchasing Organizations. As a result, in the United States, generic drug prices sometimes fall to, or even below, what it costs to manufacture the product.[8] Counterintuitively, when the number of market participants shrink, prices usually remain low because of artificial ceilings imposed by the consolidated purchasers and the Medicaid Price Inflation Rebate.[9] This dynamic has been termed "the race to the bottom."

This race to the bottom on generic drug pricing has unintended consequences—most importantly, the problem of drug shortages, which, after 14 years of persistent shortages, remains near an all-time high.[10]

This market dynamic has a two-fold impact: first, manufacturers not selected by the consolidated purchasers are forced to leave the market. Low prices reduce the ability of manufacturers to invest in quality or in newer manufacturing facilities. This also has pushed production offshore to low-wage markets where quality problems proliferate, and the FDA presence is less consistent. Manufacturers that maintain a quality culture in the U.S. or abroad will leave a market rather than lower the quality of their manufacturing processes. These realities in turn shrink the number of

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[8] U.S. generic drug prices are substantially lower than in comparator countries—a contrast with price trends for branded products. For example, generic prices in the United States are 39 percent of those in Canada, 53 percent of prices in France, 56 percent of those in Germany, and 47 percent of generic drug prices in the United Kingdom. Mulcahy, A.W., *et al*, *International Prescription Drug Price Comparisons: Estimates Using 2022 Data RAND Corporation* (2024), https://www.rand.org/content/dam/rand/pubs/research_reports/RRA700/RRA788-3/RAND_RRA788-3.pdf.

[9] For additional information on the inflationary Medicaid rebate and its negative impact on generic market sustainability, see Axelsen K, *et al.*, Charles River Associates, *An Analysis of Medicaid CPI Rebates and the Sustainability of U.S. Generic Markets* (May 2024), https://media.crai.com/wp-content/uploads/2024/05/10094459/CRA-Viatris-Generic-Sustainability-Medicaid-CPI-Rebate-May2024.pdf.

[10] American Society of Health-System Pharmacists, *Drug Shortages Statistics*, https://www.ashp.org/drug-shortages/shortage-resources/drug-shortages-statistics?loginreturnUrl=SSOCheckOnly .

market participants, lessening the resiliency of the supply chain and exacerbating the impact when something occurs to interrupt the supply of the remaining manufacturers due to quality issues, natural disasters, or disruptions resulting from geopolitical events.

Finally, low-cost manufacturing environments, such as India and China, enjoy a competitive advantage from lower labor costs, lower capital costs for new construction, less rigorous environmental standards, and government industrial policies that have directly supported the growth of the pharmaceutical sector in these countries.[11]

The government of China has developed a strategy to increase global supply chain dependencies on China, including for pharmaceuticals. The U.S. Office of the Director of National Intelligence notes a 2020 speech in which Chinese leader Xi Jinping announced an aim of "controlling key supply chains and being able to use those supply chain dependencies to threaten and cut off foreign countries during a crisis."[12]

Tariffs and Other Policies

A tariff on imported pharmaceuticals has the potential to make U.S. production more competitive. It could also disrupt supply chains and cause an acute increase in drug shortages, with potentially serious consequences for U.S. patients. In this section, we discuss the potential impact of tariffs, steps to reduce unwanted consequences, and the need for a non-tariff policy framework to accomplish the goal of sustainable domestic manufacturing.

Potential to harm patients

Generic drugs are generally manufactured and sold at thin margins that would not allow a producer to absorb a substantial tariff. Furthermore, manufacturers may be limited in their ability to pass along increased costs arising from tariffs, including by contractual relationships with group purchasing organizations, wholesalers and other supply chain partners, as well as by statutory penalties for prices that rise faster than inflation.

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[11] Word Health Organization. China policies to promote local production of pharmaceutical products and protect public health. https://iris.who.int/bitstream/handle/10665/336684/9789241512176-eng.pdf?sequence=1

[12] Office of the Director of National Intelligence. Annual Threat Assessment of the US Intelligence Community. Feb 6, 2023. https://www.dni.gov/files/ODNI/documents/assessments/ATA-2023-Unclassified-Report.pdf

A manufacturer unable to absorb or pass along a price increase due to a tariff may elect to discontinue a product, causing shortages of essential medicines. It is important to note that even if a drug is available from multiple manufacturers, an interruption in supply from one major market participant can precipitate a prolonged shortage.

To allow generic drug prices to accommodate market realities, the Department of Health and Human Services should, as outlined in the Project 2025 policy framework:

> "exempt multi-source generic drugs from requirements to pay rebates to Medicaid and other federally funded health programs, as those provisions penalize new investments in expanding manufacturing capacity when supply is unable to meet demand."[13]

With over $3 trillion in savings in the past ten years, generic competition is probably the single most effect cost-containment strategy ever developed in American healthcare. Generic drug prices often fall to 90 percent below pre-competition levels. The imposition of additional market-distorting rebates that exacerbate supply shortages is counterproductive.

Tariffs and domestic competitiveness

Raising the cost of imported medicines could increase the competitiveness of domestic generic medicines; however, as a standalone policy, tariffs will be limited in their effectiveness to drive investments in domestic manufacturing. For the lowest price products, even substantial tariffs would not result in U.S. competitiveness. For example, if a drug from overseas is currently priced at $0.50 per vial,[14] even a 100 percent tariff would not alter the economic feasibility of U.S. production. Thus, additional policy measures and strategic investments are necessary to ensure an adequate domestic generic industrial base.

Another factor limiting the effectiveness of tariffs in driving domestic investments is a lack of predictability. Building a new pharmaceutical manufacturing facility requires a major capital investment and takes a minimum of four years. Manufacturers may be reluctant to invest in an environment when future tariff policy is unpredictable. In addition, it is important to note that tariffs may also increase the costs of building and operating such facilities by raising the cost of

[13] Heritage Foundation., Project 2025 Presidential Transition Project (2023), available at https://static.project2025.org/2025_MandateForLeadership_FULL.pdf. p 457.
[14] Numerous generic drug products currently sell at or below this price range.

steel and other construction materials as well specialized manufacturing equipment, such as filling and packaging lines, or key inputs, such as drug ingredients or containers and closures (e.g. glass vials, stoppers, autoinjector pens, etc.). Tariffs on these inputs are counter to the goal of increased investment in domestic capacity.

Even transferring manufacturing of a drug product to an existing facility involves significant cost and time, an investment that a manufacturer is unlikely to make in an environment of uncertainty with no clear sustained demand for domestically produced drugs.

Sustainable domestic demand and supply resiliency

To improve the reliability and resiliency of the medicines supply chain, the Administration should incentivize drug purchasers to take into account manufacturer quality maturity, multi-year committed volume contracts, and buffer inventory, as proposed in the bipartisan discussion draft released by the Senate Finance Committee.[15] While this draft needs additional refinement to minimize administrative burden, it provides the basis for a framework that will shift the market to a more reliable supply, taking into account domestic production. Similar policy outcomes may also be achieved by executive branch action through changes to in-patient and outpatient payment programs.

ANDAs at the Ready

While U.S. dependence on foreign API is greater than U.S. dependence on foreign-manufactured finished drug product, it is essential to recognize that domestic API production is of limited value without the ability to convert API to finished drug product – and a sustainable market for those products. API is relatively low cost, compact, and shelf-stable compared with finished drug products; therefore, counterintuitively, it is easier to achieve a degree of resilience through stockpiling API than through stockpiling finished drug product.

To ensure adequate domestic capacity to convert API to the drug products that are needed by patients, the government should invest in capacity. Domestic manufacturers are unlikely to develop Abbreviated New Drug Applications (ANDAs) for essential medicines that U.S. purchasers are

[15] Senate Finance Committee. Medicare Drug Shortage Prevention and Mitigation Program. https://www.finance.senate.gov/chairmans-news/wyden-and-crapo-release-draft-legislation-to-combat-prescription-drug-shortages 03 May 2024

currently acquiring from overseas at below the domestic cost of production. However, because it requires 24 to 36 months to develop a sterile injectable drug and obtain FDA approval, waiting until the product is unavailable puts patients at risk of prolonged shortages.

To ensure that domestic manufacturers are prepared to manufacture essential medicines, the federal government should ensure that domestic manufacturers have FDA-approval and sufficient manufacturing capacity to address domestic needs. Bipartisan language in the Senate FY2025 Appropriations bill instructed the Administration for Strategic Preparedness and Response (ASPR) to prioritize ANDA development:

- Industrial Base Manufacturing and Supply Chain—The Committee urges ASPR to prioritize the development of new Abbreviated New Drug Application by a domestic manufacturer for priority essential drugs in shortage or at risk of shortage to have domestic manufacturers able to produce a drug if it goes into shortage.

In FY2026, a bipartisan appropriations letter requests $30 million for this purpose, which would support the development of approximately ten high-priority drugs.[16] This funding would support development of low-cost products that otherwise wouldn't be viable to develop, but which are at high risk of shortage in the event of a quality problem or other failure to supply by overseas companies. The Administration should include funding for development of high priority essential medicines in its budget request to Congress, and should prioritize such investments.

Capital investments

There is a qualitative difference between onshoring drugs that can be manufactured in existing facilities and drugs that require construction of new facilities. Penicillin and cephalosporin antibiotics—mentioned above as an essential and particularly vulnerable category of medicines—require dedicated manufacturing facilities to avoid cross-contamination with other drugs. Creating a new supply chain for these medicines would require the creation of multiple new facilities (e.g. dedicated API and finished dosage facilities for each drug class), at a cost of hundreds of millions of dollars per facility. Such an investment would have a negative net present value at current market prices for these products. Therefore, direct government financing will likely be necessary,

[16] Reps. Diana Harshbarger (R-TN 01) and Lori Trahan (D-MA 03). Letter to Labor-HHS Appropriations Subcommittee Chair Adderholt and Ranking Member DeLauro. 16 May 2025.

along with measures to ensure fair reimbursement, and sustained and predictable demand. Cytotoxic drugs used for cancer treatment similarly require dedicated facilities and would follow a similar pattern.

FDA Reforms

We appreciate the recent Executive Order aimed at speeding permitting and improving FDA coordination for inspections of new pharmaceutical manufacturing facilities.[17] Additional reforms can further improve the viability of the generic medicines sector.

Reducing barriers to generic drug approval can both reduce costs and improve the viability of the generic medicines sector. Once such reform would streamline the generic development and review process by providing FDA with explicit authority to disclose confirmatory formulation information to generic drug developers.[18] Under the current law, brand companies have asserted that such information constitutes trade secret disclosure—even though that information is required to be on the drug product labeling. This results in generic drug manufacturers having to submit cycles of proposed formulations through the "controlled correspondence" process that FDA rejects without comment until the generic applicant finally submits the precise formulation. This inefficient process reduces government and private-sector efficiency and is counter to the intent of the Hatch-Waxman statute that created the ANDA approval process. Last year, Congress reached bipartisan agreement to allow the FDA to conduct these sameness evaluations in an efficient and logical manner. While not yet enacted, the Administration should make a priority of this policy, which will result in faster development of new generic therapies and significant savings to the American public.

Conclusion

As for many other supply chains, the manufacture of essential medicines and their ingredients has become increasingly globalized over the past 30 years. No single policy will result in rapid

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[17] Regulatory relief to promote domestic production of critical medicines. Executive Order. 5 May 2025 https://www.whitehouse.gov/presidential-actions/2025/05/regulatory-relief-to-promote-domestic-production-of-critical-medicines/

[18] Further Continuing Appropriations and Disaster Relief Supplemental Appropriations Act of 2025, sec. 903, *available at* https://docs.house.gov/billsthisweek/20241216/CR.pdf.

reshoring. While it is important to ensure adequate domestic supply of generic drugs, the Administration must pursue a multi-pronged strategy that includes procurement practices to sustain domestic demand, targeted investments to reshore domestic manufacturing, and regulatory reforms to improve efficiency, while avoiding unintended outcomes such as increased drug shortages.

We thank you for your attention to the security of the medicines supply chain, and urge considered steps that improve supply resiliency without harm to patients.

Sincerely,

Allan Coukell

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