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December 18, 2020

BY ELECTRONIC SUBMISSION: http://www.regulations.gov
Office of Technology Evaluation, Bureau of Industry and Security
U.S. Department of Commerce

Re: Docket No. BIS-2020-0034 for "Condition of the Public Health Industrial Base and Recommend Policies and Actions To Strengthen the Public Health Industrial Base To Ensure Essential Medicines, Medical Countermeasures, and Critical Inputs Are Made in the United States"

Dear Sir or Madam,

Civica Inc. (Civica) is pleased to make the following submission in response to the Bureau of Industry request for comments, issued pursuant to Section 6(b) of Executive Order 13944, on the condition of the Public Health Industrial Base (PHIB) and to recommend policies and actions to strengthen the PHIB to ensure that essential medicines, medical countermeasures, and critical inputs are made in the United States.

Civica is a non-profit 501(c)(4) social welfare organization 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. Today, more than 50 health systems have joined Civica, representing approximately 1,200 hospitals and over 30 percent of all U.S. hospital beds.

To date, Civica has 40 sterile injectable medications under contract to supply to our member hospitals and is on track for 100 drugs by 2023. Civica also supplies the U.S. Department of Veterans Affairs, the U.S. Department of Defense and "340B" hospitals, which care for vulnerable patients in some of the most underserved areas of the country. Civica has also contributed more than 2 million vials of essential drugs to the strategic national stockpile.

Along with Civica-labeled drug from contract manufacturers, Civica is developing its own ANDA submissions and building an aseptic fill-finish facility as part of a partnership with Phlow Corporation of Virginia and the Biomedical Advanced Research and Development Authority (BARDA).

(i) The Condition of the Public Health Industrial Base (PHIB)

In recent decades, pharmaceutical manufacturing has shifted away from the United States toward countries with lower labor costs and laxer regulatory environments, such as China and India, and also to countries such as Singapore and Ireland that combine rigorous regulatory standards with advantageous tax environments and other business-friendly policies. Today, the United States is dependent on other countries for many finished drug products and active pharmaceutical ingredients (APIs). Certain APIs and many of the complex chemical precursors used to manufacture APIs are available only from China.

For more than a decade, the United States has experienced chronic shortages of essential medicines. The Food and Drug Administration (FDA)'s drug shortages list typically includes hundreds of products in shortage at any given time. This illustrates that patients are at risk from a supply chain that lacks resiliency, even absent a pandemic or other public health emergency.

However, the United States maintains substantial expertise in pharmaceutical manufacturing. A skilled workforce exists, and many plants remain in operation. Most essential drugs are off patent and available at costs that are low to moderate. With targeted investments and the right policies in place, the public health industrial base could be substantially bolstered within a decade.

(ii) Policies to strengthen the PHIB

The U.S. government has a number of tools at its disposal to strengthen the PHIB. These include:

- Use of federal purchasing power to prefer domestically manufactured drugs
- Updating the definition of domestic manufacturing to take into account the source of the API as well as the finished drug product
- Direct investments in manufacturing capacity
- Investments to support the development of advanced manufacturing technology
- Tax incentives for new manufacturing facilities located in the United States
- Streamlining permitting and approval processes to reduce the overall cost of bringing new U.S. manufacturing facilities online.

(iii) Vulnerabilities to emerging infectious diseases

While the global pharmaceutical industry responded quickly to develop vaccines and test new therapeutics, the COVID-19 pandemic has highlighted the vulnerability of the U.S. drug supply.

As the demand for essential drugs surged worldwide, several countries moved to restrict exports to ensure adequate domestic supply during early days of the pandemic.

In some countries the pharmaceutical manufacturing workforce and/or logistical and shipping personnel were unable to come to work for a prolonged period.

The shutdown of international passenger travel also reduced air cargo capacity and raised the shipping cost for critical medicines.

Amid these supply constraints, the United States was unable to rapidly scale-up production of critical medications used in the management of patients with COVID-19, in part because active ingredients and other excipients are primarily sourced external to the United States.

In addition, while secondary bacterial infection was not a major feature of this pandemic, it could easily be in response to another virus, including an influenza pandemic. Currently, the United States has no capacity to make generic antibiotics of the penicillin or cephalosporin class, which are a mainstay of medicine. While the United States uses some 65 million vials of these drugs in a normal year, and a far larger number of oral dosage forms (tablet, capsule or suspension), it currently has no facilities to make finished drugs or active ingredients, and no sources of key intermediate compounds, such as 7-aminocephalosporanic acid or 6-aminopenicillanic acid, used to create these APIs. These API precursors are made through fermentation; therefore, traditional API facilities cannot be used to manufacture them. Because both classes of drugs are allergenic, existing pharmaceutical manufacturing facilities also could not easily be converted to making finished dosage penicillin or cephalosporin products.

Moreover, the United States currently has no facilities to manufacture new innovative beta-lactam antibiotics, even those for which the research and development has been substantially supported by government investment through BARDA.

(v) Civica dependence on foreign suppliers

Civica was created to address drug shortages by ensuring a resilient supply of quality medicines at affordable prices. Therefore, Civica has always emphasized obtaining U.S.-made finished drugs and API whenever possible. If a U.S. supplier is not available, Civica prioritizes drugs from other highly regulated economies, such as European Union countries and Canada, followed by India. Chinese drugs and drug ingredients are used only when other options are not available. Of Civica's first 40 products, 88 percent are manufactured in the United States, Europe or Canada. China is the primary API source for only one product, as it is unavailable from anywhere else in the world.

Recently, BARDA announced a new partnership that will help build more U.S. advanced manufacturing capacity for essential drugs. Under this agreement, BARDA will fund Phlow Corporation, a newly formed public-benefit pharmaceutical manufacturing company in Richmond, Virginia, to build a state-of-the art continuous manufacturing facility to produce

API and API precursors. On the same site, Civica will build a facility capable of producing finished sterile injectable medicines for U.S. patients on an ongoing basis and to meet the needs of the national stockpile. This partnership will create a 100 percent U.S.-owned and operated end-to-end domestic drug manufacturing infrastructure to secure essential medicines and prevent shortages of these vital medicines in the future.

(vi) Costs, regulatory and other factors that are barriers to U.S. production

As in other industries, good paying jobs for Americans create a higher cost of labor in the United States, which is a principal factor driving pharmaceutical manufacturing overseas. In addition, regulatory costs are lower in other countries. While the United States is at a disadvantage competing against countries with lax environmental and workplace safety standards, the goal should not be to lower U.S. standards. However, policymakers should consider opportunities to streamline permitting and approval processes.

For example, in setting up a new pharmaceutical manufacturing facility, 36 months may elapse between the start of construction and the first product being released to the market. Approximately ten months of this time may be devoted to awaiting regulatory review of a product. The elapsed time may be less important in a facility that is already approved, as the lines can be used to make existing products. But the U.S. government should create a program to ensure that new facilities are reviewed as quickly as possible, while still ensuring safety. Specifically, the FDA should create a process for enhanced communication and coordination among the Office of Regulatory Affairs, the Office of Pharmaceutical Quality and the Office of Generic Drugs to streamline and prioritize inspections and approvals for new domestic facilities. Facility inspections should be carried out, by request, in advance of a regulatory submission.

Other policy changes could help level the playing field for U.S. companies competing against those from low-cost environments. Currently, any purchaser wishing to support domestic manufacturing or avoid active ingredients from high-risk countries is constrained by a lack of information. Manufacturers are not required to provide transparency on the source of the product or its active ingredient. Congress could require country of origin labeling for both finished drug and API.

Similarly, Congress should consider steps to increase publicly available manufacturer quality information. Under the current system, a purchaser has no way to assess potential differences in quality between manufacturers of approved drugs. A mature quality system requires protocols, standard operating procedures, appropriate oversight and a culture of compliance. These can be assessed and a “quality maturity” rating made publicly available. The FDA has been developing such metrics and should be encouraged to publish a working list of metrics quickly. To encourage industry participation, such metrics could be used to prioritize limited agency inspectional resources away from high-performing facilities.

(vii) U.S. government actions to foster investment and innovation

In addition to direct investment in new manufacturing capacity, procurement policy and policy changes discussed in other sections of this document, the U.S. government should use tax policy to encourage private sector investment in the PHIB. While Civica, as a non-profit, is a tax-exempt organization, policies such as tax credits and accelerated depreciation would benefit other manufacturers.

To encourage domestic production, including relocation of manufacturing for existing approved drugs, policymakers should consider waiving FDA user fees and inspection fees for drugs on the essential medicines list.

(viii) Automation and other productivity-enhancing technologies

Advanced manufacturing is a term for newer technologies that will help improve the speed and flexibility of drug manufacturing. This approach offers several advantages, including:[1]

- Precise control of product quality
- Ability to rapidly respond to changes in demand
- Lower cost of production
- Reduced environmental impact

Despite the promise, continuous manufacturing has been adopted only to a limited extent, particularly for older, off-patent drugs. In part, the low return on these products generally does not justify an investment in new facilities or methods.

The U.S. government could further support the development of advanced manufacturing by supporting the creation of Centers of Excellence and providing expedited FDA review when a technology is likely to prevent or resolve a drug shortage, assist in maintaining an adequate supply of critical medications for national emergencies, or promote the adoption of innovative approaches to drug product design and manufacturing.

(ix) Federal funding to support the PHIB

As noted above, Civica and Phlow Corporation are the beneficiaries of BARDA funding to build new U.S pharmaceutical manufacturing capacity. While the funding is substantial ($354

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[1] Statement of Janet Woodcock, MD, U.S. Food and Drug Administration, October 30, 2019. https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Testimony-Woodcock-API_103019.pdf. Accessed May 20, 2020.

million to support construction of two facilities), it will support end-to-end manufacturing of numerous generic drug products. The U.S. government should assess domestic supply for drugs on the essential medicines list and make targeted investments to ensure that a U.S. manufacturer exists, and that production can be ramped up in the event of an emergency. Federal grants should support construction, alteration or renovation of facilities for the U.S.-based manufacture of medicines on the essential medicines list. In some cases, where essential drugs can't be made at a competitive price in the United States, consideration should be given to providing ongoing operational support as an "insurance policy" to ensure that this capacity exists when it is needed.

Use of the Development Finance Corporation to provide low-interest loans to support domestic pharmaceutical manufacturing is also an approach with potential. Consideration should be given to broadening DFC financing from a narrow list of APIs to the broader set of drugs on the essential medicines list.

(x) Procurement policy

Executive Order 13944 establishes a purchasing preference for domestically manufactured drug products on the Essential Medicines list. This list of 223 drug and biological products and 96 device countermeasures includes medicines used in the management of patients in intensive care and on ventilator support. It includes a range of antimicrobial and antiviral drugs, as well as medical countermeasures for a wide range of chemical, biological and radiological threats. Many of the drugs on the list have already appeared on FDA's drug shortages list, underlining the need to ensure robust supplies and manufacturing capacity.

The EO allows a price premium for U.S.-made drugs of 25 percent and provides a variety of safety clauses of U.S. purchasing would cause shortages or be otherwise detrimental. The U.S. government should have a goal of having at least one U.S. supplier for every product on the list and should track and report annually on progress toward that goal.

In addition, to maximize the effectiveness of this preferred procurement approach, the government should be willing to enter long-term supply contracts. The availability of, for example, a five-year-long contract would provide stability of revenue that would help support a decision to invest in U.S. manufacturing.

Policymakers should also ensure that the definitions of domestic manufacturing are consistent with the goal of making not just the finished drug formulation, but also the active ingredient domestically. One change Congress could make, as proposed in recent legislation, would be to amend the Trade Agreements Act of 1979 to clarify that pharmaceutical products would not be considered to have originated in a country if the API originated in a different country. Updating this definition would reverse a recent court decision, *Acetris Health, LLC v. United States*, that precludes U.S. government purchasers from giving preference, under the Buy

American Act, to pharmaceutical products that originated entirely within the United States or our preferred trading partners.

Another approach, specific to the Department of Defense, would be to include essential drugs under a "Berry Amendment" provision. This provision establishes "domestic source restrictions that prohibit DOD from acquiring food, clothing, fabrics (including ballistic fibers), specialty metals, stainless steel, and hand or measuring tools that are not grown or produced in the United States."[2]

To create a far greater pull incentive for domestic production, federal procurement policy for essential drugs should go beyond DOD, the Veterans Administration and the Strategic National Stockpile, to include purchasing by other public programs. Were Medicare and Medicaid—combined, the largest purchaser of prescription drugs in the world—to prefer U.S-made drugs on the essential medicines list, even absent a price premium, it would transform the market and substantially increase investment in the PHIB.

(xi) Workforce

Pharmaceutical manufacturing is complex and relies on a highly skilled, multidisciplinary workforce that includes chemical engineers, materials scientists, quality personnel, operations specialists, compliance staff and a wide range of other specialized staff. Nevertheless, Civica does not believe that targeted workforce investments are needed to ensure the PHIB. Rather, with the creation of a viable economic model for domestic manufacturing, the workforce will follow.

(xii) Ensuring adequate redundancy

Having redundant manufacturing facilities for any drug builds robustness into the supply chain, and will come at a cost. The government should create incentives mentioned earlier to create additional redundant manufacturing facilities. For example, a drug could be made by one company but in two geographically different manufacturing locations or by two completely different manufacturers.

(xiii) Key actions to ensure long-term demand

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[2] Congressional Research Service. The Berry Amendment: Requiring Defense Procurement to Come from Domestic Sources. Feb 24, 2014

The market for generic essential medicines is characterized by short-term demand and pursuit of the lowest possible price. This reduces the incentive for companies to invest in quality systems, new manufacturing techniques or redundancy. It creates instability in the market and fuels shortages even under normal circumstances. In order to stabilize supply, Civica has entered long-term (5-year) supply contracts with its member hospitals and suppliers. Similar guaranteed volume and price agreements would help ensure the viability of products produced in the United States and protect investments in manufacturing against low-priced imports of the same medicine.

(xiv) Key actions to maintain and maximize domestic production of critical inputs, finished drug products and finished devices

Beyond finished drugs and APIs, most of the fine complex chemical intermediates used to make API are synthesized overseas. That puts the U.S. drug supply at risk from supply disruptions. However, by one analysis, chemical intermediates typically account for less than two percent of the cost of a finished generic drug.[3] As noted above, Civica is part of a partnership with Phlow Corporation, which will manufacture API and API precursors in the United States. More of these critical inputs could be manufactured domestically, but pharmaceutical companies are unlikely to change their supply chains without some external impetus. Consideration should be given to this supply chain vulnerability and to ensuring adequate stockpiles and/or U.S. manufacturing capacity.

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The goal of policies to strengthen the PHIB is not to disentangle the United States from the global marketplace. A diverse drug supply chain is a good insurance policy. But for essential drugs, in peacetime or pandemic, the United States should ensure that it can provide the medicines Americans need, when they are needed.

Thank you for the opportunity to provide input on these important questions.

Sincerely,

Martin VanTrieste
President and Chief Executive Officer
Civica Inc.

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[3] Allen Erickson, CEO, Lacamas Laboratories (personal communication)