

# DAY ONE PROJECT

A Federal Adaptive On-Demand  
Pharmaceutical Manufacturing  
Initiative

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## Summary

The COVID-19 pandemic has highlighted the urgent need to address lags in American pharmaceutical manufacturing. An investment of \$5 billion over five years will improve U.S. pharmaceutical manufacturing infrastructure, including the development of new technologies that will enable the responsive, end-to-end, on-demand production of up to half of the Food and Drug Administration (FDA) list of 223 essential medicines by year two, and the entire portfolio by year five. Spearheading improvements in domestic manufacturing capacity, coupled with driving the advancement of new adaptive, on-demand, and other advanced medicine production technologies will ensure a safe, responsive, reliable, and affordable supply of quality medicines, improving access for all citizens, including vulnerable populations living in underserved urban communities, rural areas, and tribal territories.

## Challenge and Opportunity

### Urgent Need to Strengthen U.S. Pharmaceutical Manufacturing

COVID-19 has served as a wake-up call and an opportunity to bring pharmaceutical manufacturing into the 21<sup>st</sup> century. Production factory closures, shipping delays, shutdowns, trade limitations, and export bans have severely disrupted the supply chain. Yet the demand for vaccines and COVID-19 treatment options worldwide continues to increase. However, recent advances in manufacturing technology can be deployed to create a 21<sup>st</sup> century domestic pharmaceutical manufacturing economy that is distributed, flexible, and scalable, while producing consistent high-quality medicines that Americans rely on.

To improve national security and achieve the goal of medicine production self-sufficiency, the Biden-Harris Administration has an opportunity to address legacy issues plaguing the pharmaceutical manufacturing industry and usher in a technology revolution that will leapfrog our legacy 19<sup>th</sup> century industrial manufacturing processes. The Biden-Harris Administration should prioritize:

- **Improving the domestic production of small-molecule medicines, including Key Starting Materials (KSMs) and Active Pharmaceutical Ingredients (APIs) in order to reduce dependence on foreign manufacturers.** China and India together supply 75-80 percent of the APIs imported to the U.S.<sup>1</sup> In March, during the largest spring spike in U.S. COVID-19 cases, India restricted the export of 26 APIs as well as finished pharmaceuticals. The U.S is the leading market for generic pharmaceuticals, with 9 out of every 10 prescriptions filled being for generic drugs in 2019, and a projected

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<sup>1</sup> Mordor Intelligence, *Active Pharmaceutical Ingredients (API) Market - Growth, Trends, Covid-19 Impact, and Forecasts (2021 - 2026)*. (Mordor Intelligence, 2020).

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market value of \$415 billion by 2023.<sup>2</sup> An aggressive race to the bottom in terms of price has driven the vast majority of supply chain manufacturing overseas, where lower production costs and government subsidies, particularly for exports, benefit foreign suppliers.

- **Improving the scale, efficiency, and effectiveness of domestic biopharmaceutical manufacturing.** The past decade has ushered in a significant shift in the nature of pharmaceutical products: there is now a greater prevalence of large molecule drugs, personalized therapeutics, and a rise in treatments for orphan diseases. New approaches to developing vaccines, such as the mRNA COVID-19 vaccine, are setting a new paradigm for future vaccines using DNA, RNA, adenoviruses, and proteins. There is an urgent need to scale up the domestic manufacturing of biologics, including vaccines, to address biomedical threats. In addition, innovation in manufacturing technology is critical to improving both scalability and time to market. New technology will improve yields while lowering costs and reduce waste through green chemistry.

Additional benefits associated with establishing a robust domestic manufacturing base, including distributed manufacturing capability, include:

- **Reducing vulnerabilities associated with an over-reliance on centralized manufacturing and processing models.** In the food industry, a COVID-19 outbreak in just a few chicken and pork processing plants led to a nationwide shortage of these important foods. A more flexible, resilient distributed manufacturing model, such as one utilizing additive manufacturing and 3-D printing, would have prevented the need for such a disruptive response. 3-D printing, for example, has successfully delivered more than 1,000 parts to local hospitals during the pandemic.<sup>3</sup>
- **Improving the reliability of facilities and the quality of products for the U.S. market** through the development and deployment of advanced manufacturing technologies. Low-cost, offshore manufacturing raises quality risks; more than half of FDA warning letters issued between 2018 and 2019 were sent to facilities in India or China.<sup>4</sup> There are numerous examples of risks to both the health and security of U.S. citizens in the recent past. In 2007, a Chinese company deliberately contaminated the blood thinner Heparin and 246 Americans died. In 2015, the FDA banned 29 products after inspecting a Chinese pharmaceutical factory, although it exempted 14 products over U.S. shortage concerns.

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<sup>2</sup> IQVIA Institute for Human Data Science, *The Global Use of Medicine in 2019 and Outlook to 2023: Forecasts and Areas to Watch* (IQVIA, Jan 2019).

<sup>3</sup> Hewlett Packard, "HP Inc. and Partners Mobilize 3D Printing Solutions to Battle COVID-19," <https://press.hp.com/us/en/press-releases/2020/hp-inc--and-partners-mobilize-3d-printing-solutions--to-battle-c.html>, (2020).

<sup>4</sup> Ben Hargreaves, "Analysis finds bulk of warnings delivered to Indian and Chinese drug makers," *Outsourcing-Pharma* (August 30, 2019).

And in 2018, a Chinese vaccine maker sold at least 250,000 substandard doses of vaccine for diphtheria, tetanus, and whooping cough.<sup>5</sup>

- **Improving access for vulnerable populations** living in underserved urban communities, rural areas, and tribal territories. COVID-19 created unprecedented pressure on the federal system when requests from 56 State, Local, Tribal, and Territorial (SLTT) authorities nearly simultaneously requested medical supplies. According to testimony presented by the RAND Corporation, the quantities of material in the Strategic National Stockpile (SNS) were not nearly enough to fill all of the requests, resulting in a heated competition and a failure to deliver products to all of the different parts of the United States equitably.<sup>6</sup>
- **Reducing critical drug shortages** that have plagued U.S. health systems for more than a decade. With COVID-19 cases on the rise, and hospitalizations increasing in more than 40 states, critical drug supplies are waning, with 29 out of 40 drugs used to combat the coronavirus currently in short supply.<sup>7</sup> In addition, 43% of 156 acute care medicines used to treat various illnesses are running low.<sup>8</sup> In 2019 the U.S. experienced 186 new drug shortages; 82% of which were classified as being due to “unknown” reasons, largely because of the intentional opacity and secrecy of the upstream supply chain.<sup>9</sup> According to the Center for Infectious Disease Research and Policy (CIDRAP) the U.S. health system spends more than \$500 million a year on estimated costs related to drug shortages, with approximately \$200 million in direct costs and up to \$360 million on indirect costs.<sup>10</sup>
- **Stabilize pricing** by enabling ‘just in time’ manufacturing capability that reduces the need to stockpile large supplies of medicines and is more responsive to surges in demand. Furthermore, complex supply chains, procurement mechanisms, and the consolidation of U.S. buyers create ‘pay-to-play’ schemes that contribute to chronic drug shortages by driving manufacturers out of the market and contribute to price volatility. New technologies that enable responsive and efficient approaches to surges in demand, or to address drug shortages, will also stabilize pricing over time. Today, one in four Americans cannot afford their medication.<sup>11</sup> Mylan, for example, increased the price of EpiPen by more than 500%, from \$94 for a two-dose pack in 2007 to \$608 in 2018.<sup>12</sup>

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<sup>5</sup> Javier C. Hernandez, “In China, Vaccine Scandal Infuriates Parents and Tests Government, *The New York Times* (July 23, 2018).

<sup>6</sup> Daniel M. Gerstein, *The Strategic National Stockpile and COVID-19: Rethinking the Stockpile*, Testimony presented before the Senate Committee on Homeland Security and Governmental Affairs on June 24, 2020 (Santa Monica: RAND Corporation, 2020).

<sup>7</sup> University of Minnesota Center for Infectious Disease Research and Policy (CIDRAP), “Part 6: Ensuring a Resilient US Prescription Drug Supply,” *COVID-19: The CIDRAP Viewpoint* (Regents of the University of Minnesota, 2020).

<sup>8</sup> University of Minnesota Center for Infectious Disease Research and Policy (CIDRAP), “Resilient Drug Supply Project: Critical Acute Drug List & Critical COVID-19 Drug List Drug Shortages Reported by ASHP & FDA (University of Minnesota CIDRAP, Resilient Drug Supply Project, and PRIME Institute, 2020). <http://freepdfhosting.com/79b4b318ec.pdf>

<sup>9</sup> American Society of Health-System Pharmacists (ASHP), “National drug shortages: active shortages by quarter, June 30, 2020,” as reported in Drug Shortage Statistics.

<sup>10</sup> University of Minnesota CIDRAP, “Part 6: Ensuring a Resilient US Prescription Drug Supply”.

<sup>11</sup> “The Crisis,” The Campaign for Sustainable Rx Financing, <https://www.csrpx.org/the-crisis/>.

<sup>12</sup> “Infographic: Mylan Price Hikes,” The Campaign for Sustainable Rx Financing, <https://www.csrpx.org/resources/infographic-mylan/>

## 21<sup>st</sup> Century Problems Require 21<sup>st</sup> Century Solutions

Advanced manufacturing technologies such as continuous flow, which allows for drugs to be produced in a continuous stream, can reduce the time it takes to manufacture a drug and ensure quality through advanced controls and process analytic technologies. These technologies can enable remote monitoring during production and real-time release testing. In addition, miniaturized manufacturing units that could easily fit in existing pharmacies would facilitate a distributed network for producing medicines that is flexible enough to rapidly pivot and make any therapeutic required for national security or emergency preparedness with short lead times. A distributed network of on-demand pharmaceutical manufacturing devices will improve supply availability without the need to stockpile large quantities of medications.

Automation will play a key role in advanced pharmaceutical manufacturing, as will 3-D printing. Automation will reduce manufacturing overheads and ensure quality, scalability, and increased outputs. It allows advanced connectivity of equipment, people, processes, services, and supply chains. The 3-D printing of pharmaceutical products, meanwhile, is accelerating following the FDA's approval of the first 3-D printed drug in 2015. This technology accommodates personalized doses and dosage forms and other emerging technologies that enable bespoke tablet sizes, dosages, and forms (suspension, wafers, gel strips, etc.) to optimize patient compliance and ease of use. Another major advantage is the possibility of redistributed manufacturing—printing medicine much closer to the patient. 3-D printing and on-the-spot drug fabrication will have major implications in medical countermeasures and for medications with limited shelf-life.

Finally, investing in advanced biopharmaceutical manufacturing infrastructure and innovation would establish the capacity to produce domestically through a network of high-tech, end-to-end manufacturing and development solutions, which will ensure that the medicines of today and tomorrow, such as new vaccines, can be made quickly, safely, and at scale.

## **Plan of Action**

The Biden-Harris Administration should launch a national adaptive pharmaceutical manufacturing initiative focused on the ambitious goal of achieving medicine production self-sufficiency. The Presidential Initiative should be led by an Ambassador who reports to the Secretary of Defense. The Secretary of Defense is already leading a whole-of-government effort to assess risk, identify impacts, and propose recommendations in support of a healthy manufacturing and defense industrial base – a critical aspect of economic and national security. The Department of Defense (DoD) coordinates these efforts in partnership with the Departments of Commerce, Labor, Energy, and Homeland Security, and in consultation with the Department

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of the Interior, the Department of Health and Human Services (HHS), the Director of the Office of Management and Budget, and the Director of National Intelligence.

Clear deliverables and timeline-dependent milestones are critical to the success of this initiative. New local manufacturing solutions — such as state-of-the-art facilities and devices for automated end-to-end pharmaceuticals to be deployed in a trailer — can augment ongoing efforts to reduce manufacturing ramp-up time, the need for strict environmentally controlled secure storage facilities, and waste from expired medications. Having stand-alone or mobile devices for automated end-to-end pharmaceuticals would empower local authorities to manage delivery and distribution protocols, ensuring that local populations have the lifesaving medicines they need when they need them.

To this end, the DoD, in collaboration with HHS and the FDA, should launch a national initiative to increase U.S. manufacturing capacity and accelerate the development of new technology, with an emphasis on the adoption of advanced analytical capabilities to ensure quality. These platforms should be able to produce precursors, APIs, and final drug products (small molecule and biologics) in multiple forms, enabling rapid response priority medicines on demand, targeting the creation of a self-sustaining domestic supply chain of the 223 medicines on the FDA Essential Medicines list, as well as new vaccines and medicines coming off patent in the next 5 years.

The establishment of a national pharmaceutical manufacturing network will facilitate a U.S. strategic asset that changes how we source, manufacture, and distribute medicines. This robust domestic network will mitigate drug shortages, ensure quality, and allow rapid response to emergency scenarios. Importantly, it re-establishes a domestic pharmaceutical manufacturing industry that relies less on overseas suppliers, advances our country's innovation prowess, and will create thousands of new U.S. jobs.

## Recommendations for the Department of Health and Human Services and the Department of Defense

To enable a more resilient, responsive and adaptive U.S. pharmaceutical supply chain and achieve medicine production self-sufficiency, the following actions are recommended.

First, sign an executive order that directs the formation of a Joint Interagency Task Force (JIATF) DoD, HHS and FDA, led by a Presidential appointee (Ambassador), with a \$5 billion, 5-year funding commitment, to establish a more robust domestic responsiveness that includes advanced manufacturing technologies for biologics and small molecules. A key objective of the executive order and the formation of a JIATF is to ensure the U.S. can produce medicines stateside with improved responsiveness.

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This initiative will:

- Identify a portfolio of products that can be rapidly deployed at a national, state or local level utilizing advanced manufacturing platforms, identify associated research and development agenda needs, and determine how this aligns with other initiatives such as the Strategic National Stockpile.
- Support targeted synthetic biology research and development to enable faster manufacturing of low-cost, on-demand vaccines and precision immunotherapies.
- Support the advanced development of green, modular, on-demand small-molecule manufacturing technologies that would accommodate small batch lines, with an ability to scale and produce higher volume when needed.
- Support targeted advanced development of sensor technologies that can monitor on-line and real-time quality control.
- Support the acquisition and/or establishment of new U.S.-based manufacturing facilities.
- Support green technology solutions.
- Establish a center for excellence in advanced manufacturing at the FDA, to support and advance regulatory science.
- Identify new business models to support the economically sustainable domestic adoption and deployment of new manufacturing technology.
- Enact push and pull incentives to direct new medical countermeasure development funded by HHS (Biomedical Advanced Research and Development Authority, BARDA) and other federal agencies to utilize adaptive manufacturing practices as appropriate.

Key milestones and deliverables of this initiative include the following. (1) By year 2, ensure that 50% of the FDA's Essential Medicines are manufactured from end-to-end in the United States, to include starting materials and APIs. (2) By Year 5, the FDA will have the capability to manufacture all Essential Medicines in the United States. (3) In this same time frame, the quality of every dose of the medicines produced can be provided to the FDA for oversight. (4) All starting materials are sourced domestically or from trusted allied nations.

## Conclusion

Expanding critical U.S. pharmaceutical manufacturing infrastructure and establishing an adaptive, transparent on-demand pharmaceutical manufacturing capability guarantees safe, secure, high-quality, and reliable supply of affordable drugs and would create thousands of new U.S. high-paying jobs. By utilizing green technology, it could reduce hazardous material waste by as much as 30 percent over conventional manufacturing. It would also improve transparency and supply chain efficiencies that could reduce shortages, lower costs, and improve the quality of medicines. A distributed, modular, on-demand manufacturing network capable of making biologics and small molecules cannot be disrupted by the loss of centralized facilities, natural disasters, pandemics, or adversarial actions. New local on-demand manufacturing solutions will

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reduce manufacturing ramp-up time, the need for strict environmentally-controlled secure storage facilities, and waste from expired medications. It will empower local authorities to manage delivery and distribution protocols, ensuring that local populations have the lifesaving medicines they need when they need them. In addition, it would offer the potential to improve warfighter resilience and recovery by providing the groundwork for producing medicines on demand, and at the point of care, whether it be on a C-5, submarine, or at a forward combat support hospital.



## Frequently Asked Questions

### **Who can participate?**

Any U.S. public or private organization may apply.

### **How will the money be spent?**

Funding will support new technologies and the scale-up of a robust domestic manufacturing base that guarantees a reliable, adaptive, efficient manufacturing process with an emphasis on the production of high-quality, affordable medicines. The funding will also support innovative business models that improve access, reduce costs, and incorporate advanced quality systems.

### **How will this initiative collaborate with pharmaceutical companies?**

The pharmaceutical industry is critical to ensuring the goal of this initiative. They may participate directly in a competitive bidding process or may choose to enter into partnerships with private or public organizations.

### **How do you recruit the talent necessary to serve this initiative?**

Workforce development will involve individuals from trade schools through advanced degree programs.

### **What coordination challenges do you foresee between government and industry?**

Major public-private initiatives, such as the one proposed, comprise trans-organizational systems (i.e., partnerships, alliances, or coalitions) that enable, and are reliant upon, the joint decisions and actions of participating organizations, each of which maintains its individual identity and goals. Trans-organizational systems are non-hierarchical structures that service a megacommunity in the collective pursuit of a goal. Governance models for trans-organizational systems require higher levels of coordination, cooperation, and collaboration than traditional organizations because of the independence, diversity, and number of actors and extended timeframes involved.

In this regard, it is critical that the leadership of this new initiative gather insight, and work closely, to understand where the opportunities are within industry today, as well as a line of sight on where new technologies are emerging that may have a transformative impact. The challenge is to create incentives that will enhance collaboration and transparency among stakeholders and to have clear, time-bound and measurable goals to ensure accountability.



### About the Author

Dr. Geoffrey Ling is the CEO of On Demand Pharmaceuticals, which is developing manufacturing technology for point-of-care end-to-end generic pharmaceutical production. He is a pharmacologist, neuro-intensive care physician and Professor at Johns Hopkins Hospital, former founding Director of the Biological Technologies Office at DARPA and former Assistant Director for Medical Innovation in President Obama's Office of Science, Technology and Policy (OSTP). Dr. Ling is a retired U.S. Army colonel physician who served in both Iraq and Afghanistan. More information about Dr. Ling can be found

at: [https://en.wikipedia.org/wiki/Geoffrey\\_Ling](https://en.wikipedia.org/wiki/Geoffrey_Ling)



### About the Day One Project

The Day One Project is dedicated to democratizing the policymaking process by working with new and expert voices across the science and technology community, helping to develop actionable policies that can improve the lives of all Americans, and readying them for Day One of a future presidential term. For more about the Day One Project, visit [dayoneproject.org](http://dayoneproject.org).