PUBLIC PRODUCTION AND PUBLIC HEALTH

Written statement of Melissa Barber, Ph.D.
Postdoctoral Fellow
Yale School of Medicine, Yale Law School, and
Yale Collaboration for Regulatory Rigor, Integrity, and Transparency (CRRIT)

U.S. Senate Committee on Armed Services, Subcommittee on Personnel Hearing:
The Department of Defense's efforts to ensure servicemembers' access to safe, high-quality pharmaceuticals

Tuesday, April 30, 2024, 2:30 PM

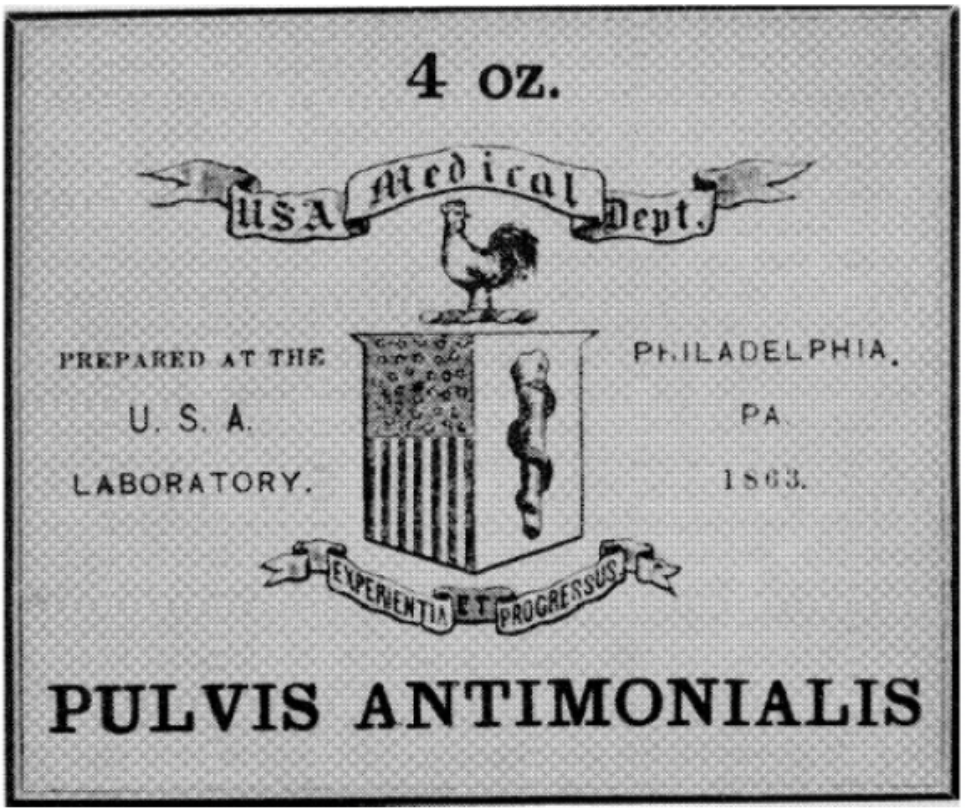


Figure 1. Label for a drug manufactured for defense medical use at one of the earliest known government-owned, government operated (GOGO) facilities. Philadelphia, 1863.[1]

OUTINE OF WRITTEN TESTIMONY

1. The availability and affordability of drugs is a pressing challenge faced by the Department of Defense.

1.1 The root causes and proximate determinants of shortages are complex and heterogeneous. Any solution will require a long-term collaborative strategy by many government departments.

1.2 The Department of Defense's ability to provide quality healthcare has been compromised by pharmaceutical supply issues.

1.3 At the same time, the Department of Defense is facing increases in prescription drug costs, which have outpaced inflation.

1.4 The increasing market concentration of key starting material (KSM) and active pharmaceutical ingredient (API) manufacturing is an important driver of shortages. Reversing this trend will require long-term strategies and investment to diversify supply and increase domestic capacity.

1.5 Increasing the prices paid for drugs is neither an efficient nor effective strategy to prevent future shortages, unless tied to conditionalities requiring manufacturers to demonstrate investments that address the underlying causes of shortages (e.g., improving risk management practices, diversifying supply sources, investing in back-up manufacturing capabilities, and other reforms to improve supply chain robustness.)

2. Meeting defense health needs in a mixed economy: past lessons and future directions.

2.1 Public sector R&D has yielded breakthroughs of immense military (and wider public health) significance.

2.2 However, the public sector does not just undertake R&D: there is a long history of the public sector also stepping in to manufacture drugs for military use.

2.3 Contractor-owned, contractor operated (COCO) facilities have sometime been characterized as cost-saving and lower risk compared to government-owned, contractor-operated (GOCO) or government-owned, government operated (GOGO) alternatives. However, COCO models have not always resulted in the desired efficiencies, and have in some cases resulted in preventable morbidity and mortality among people serving in the military.

2.4. GOGO and/or GOCO facilities have been recommended for decades as a solution to DOD supply challenges and pursued on a bipartisan basis.

2.5 Congress should consider introducing legislation establishing clear options for creating a government-owned facility to manufacture priority health products to meet DOD needs. Such a facility would ensure reliable access to quality drugs for servicemembers, as well as generate significant cost savings.

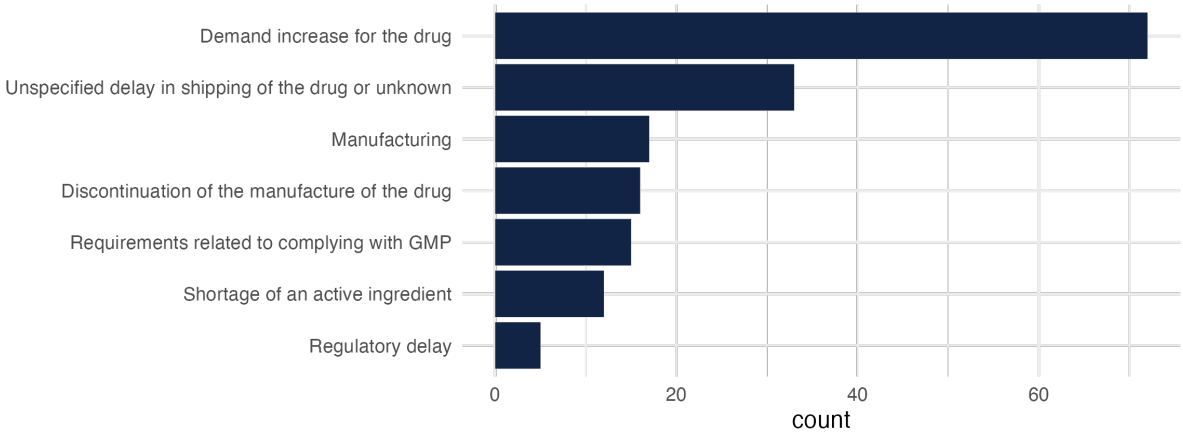
1. The availability and affordability of drugs is a pressing challenge faced by the Department of Defense (DOD).

1.1 The root causes and proximate determinants of shortages are complex and heterogeneous. Any solution will require a long-term collaborative strategy by many government departments.

Both academics and US government bodies, including the FDA and Government Accountability Office (GAO), have studied the causes of shortages, but analyses are limited by incomplete data. As of April 2024, there were 131 drugs reported to the US Food and Drug Administration (FDA) to be in shortage.[21]

Manufacturers report shortages to the FDA, but there are no standardized shortage reporting codes, nor are manufacturers obligated to give detailed information on the cause(s) of the shortage. The accuracy and diligence in shortage reporting is not audited by the FDA. A quarter of current reported shortages (April 2024) did not have a declared cause (Figure 2).[2] Among those with a reported cause, the majority (53%) were due to increased demand, followed by discontinuation of manufacture (12%), manufacturing delays or other issues (12%), good manufacturing practices (GMP) issues (11%), shortage of active pharmaceutical ingredient (API) (9%), and regulatory delays (4%) (Figure 2).[2]

Figure 2. Current shortages reported to the FDA by declared cause[2]



While some shortages are resolved quickly, others last years (Figure 3). At least 9 drugs have been in shortage since 2016, of which 6 have been in shortage since 2012 (Table 1).[2]

[1] Number of drugs counted as based on unique generic name or active ingredient, as reported by FDA. Data as downloaded 12 April 2024.

Figure 3. Current shortages reported to the FDA by year the shortage was first reported[2]

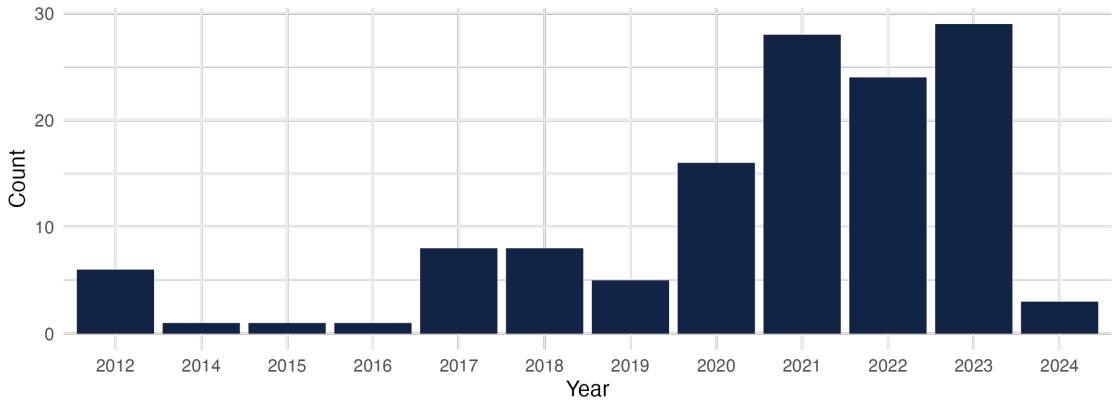


Table 1. Drugs with unresolved drug shortages reported to the FDA: subset with initial shortage reported 2012-2016.

Drug and formulation	Reported cause of shortage	Year first reported
Atropine Sulfate Injection	Manufacturing; Requirements related to complying with GMP	2012
Epinephrine Bitartrate, Lidocaine Hydrochloride Injection	Demand increase for the drug; unspecified "delay in shipping of the drug" (2016)	2012
Epinephrine Injection, Syringes	Manufacturing; Demand increase for the drug	2012
Fentanyl Citrate Injection	Discontinued	2012
Leucovorin Calcium Injection	Demand increase for the drug	2012
Lidocaine Hydrochloride Injection	Demand increase for the drug	2012
Cefotetan Disodium Injection	Unspecified delay in shipping of the drug, discontinued (2015)	2014
Cefotaxime Sodium Injection	Demand increase for the drug	2015
Sodium Acetate Injection	Manufacturing	2016

In 2021, the Department of Health and Human Services (DHHS) conducted a review of API and pharmaceutical supply chains, as part of a 100-day review under Executive Order 14017 on America's Supply Chains.[3] The report identified five factors contributing to risk in the supply chain, including:

"*1) The complexity, vastness, and multinational nature of drug supply chains and the corresponding overdependence on foreign entities who may prioritize national interests above trade in an emergency.*
2) Reduced incentives for existing manufacturers to invest in upgrading equipment, improving supply chains, or expanding capacity.
3) Lack of redundant capacity in manufacturing.
4) Just-in-time inventory management practices that limit inventory and reduce the ability to respond to surges in demand.
5) Geographic concentration of manufacturers that puts production at risk from natural disasters or climate change that can quickly affect an entire region."[3]

1.2 The Department of Defense's ability to provide quality healthcare has been compromised by pharmaceutical supply issues.

The Defense Health Agency (DHA) is subject to similar market forces as wider commercial markets.

The 2023 *Report on the Department of Defense Pharmaceutical Supply Chain Risks* by the Office of the Under Secretary of Defense for Acquisition and Sustainment reported that the Defense Logistics Agency (DLA) spent $5.4 billion per year on pharmaceuticals, accounting for 2% of the total US commercial market.[4] Similarly, the 2023 Biodefense Posture Review concluded that "compared to the global market, DoD's unique biodefense demands are small and not commercially competitive."[5]

In testimony to the U.S.-China Economic and Security Review Commission hearing on *Exploring the Growing U.S. Reliance on China's Biotech and Pharmaceutical Products,* Christopher Priest (Principal Deputy, Deputy Assistant Director of Healthcare Operations at the Defense Health Agency) described DOD's reliance on the commercial market, and the limitations of its relatively small buying power in shaping markets:

*"**DoD is wholly dependent upon the consumer market** to produce and distribute the pharmaceutical products it requires to ensure the health, safety and wellbeing of the DoD personnel and beneficiaries who require them…Given its relatively small footprint in the commercial marketplace, DoD must work within the constraints of the commercial sector and the market forces that drive and shape it. **Depending on the commercial sector, it is a two-edge sword. While it enables DoD to reap the efficiencies of the competitive commercial marketplace, it also makes DoD totally dependent on the sources that competition produces.** These sources are increasingly foreign and non-compliant with the Buy American Act, as amended by the Trade Agreements Act of 1979. **DoD's compliance with these acts drives up DoD pharmaceutical costs while having little or no effect on the primary production arc of the commercial sector,** which is bending toward foreign production sources." (emphasis added).*[6]

Challenges reported by DOD also extend to limited visibility in mapping API capacity and supply sourcing: the DOD reported to the Senate Committee on Homeland Security and Governmental Affairs that it lacks "authoritative data" on the sources of drugs purchased from the private sector.[7] The same report noted that the DLA was "unable to determine with certainty if any of the drugs it purchases rely solely on sources in China or India", with the exception of three drugs.[7]

One recent examples of shortages in the commercial market impacting members of the military and their families is penicillin G benzathine. Pfizer first reported a shortage of penicillin G benzathine injections in June 2023.[2] According to the FDA, penicillin G benzathine has been on the shortages list since at least 2012.[2] The FDA reports that the drug is still in shortage as of April 2024.[2] Penicillin G benzathine is given prophylactically to military recruits during boot camp.[8] The drug is also used for syphilis and various streptococcal infections, including in the treatment of rheumatic fever to prevent the development of rheumatic heart disease. Pfizer has stated that they anticipate shortages of the pediatric formulation because the pediatric supply line has been repurposed to manufacture the adult formulation.[8]

TRICARE publishes its formulary; however, I am not aware of a public, current database of DOD direct pharmaceutical purchases.[9] I have instead reviewed all pharmaceutical contracts available on the System for Award Management (SAM.gov) and cross-checked them against drugs currently listed as "in shortage" by the FDA (as of April 2024).[2] See Table 2.

Another challenge of DOD's reliance on commercial markets is markets for some health products are small, and in some cases DOD is a monopsony purchaser. Recent DOD contracts with sole source notices (as required by U.S.C. 2304 (c)) include TPOXX (tecovirimat for orthopoxviruses such as smallpox and mpox), pre-mixed intravenous IV fluids, and neonatal pediatric inhaled nitric oxide gas. Review of recent DOD health purchase contracts also highlights DOD health product needs unlikely to be found in commercial markets, for example contracts for battlefield-suitable analgesic autoinjectors, nerve agent treatment autoinjectors, and medicines used by US Navy Marine Mammal Program-trained California sea lions and bottlenose dolphins.

Table 2. Current drug shortages and year of confirmed last DoD purchase

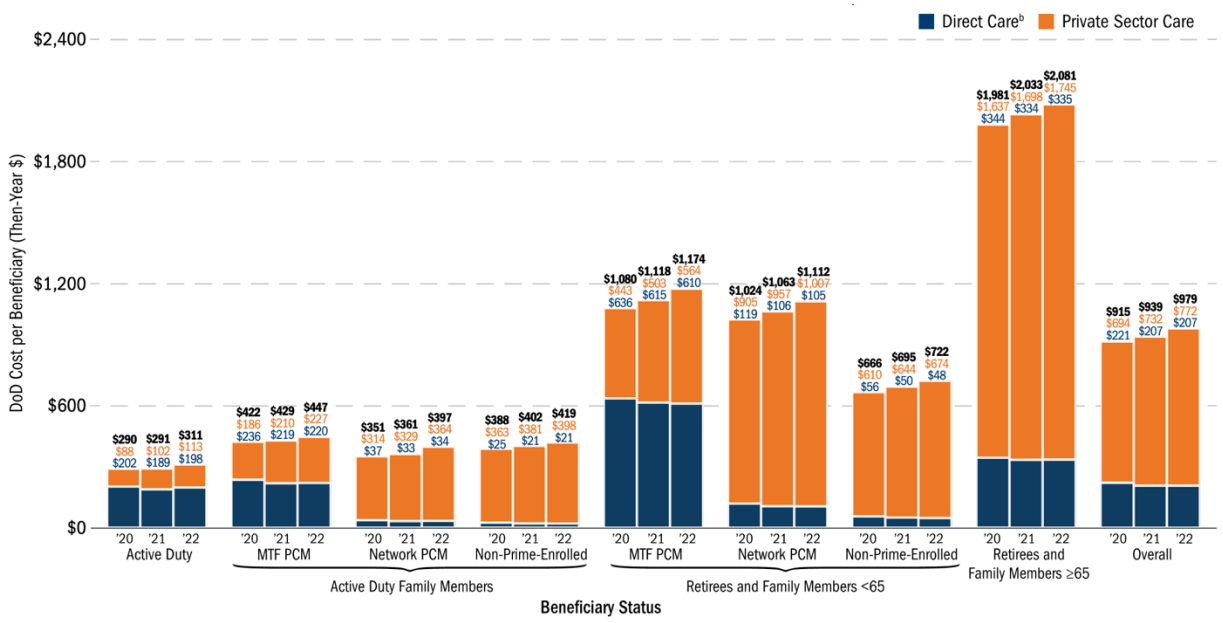
Drug currently in shortage (FDA, April 2024)	Last known purchase by DOD (sam.gov)
Albuterol Sulfate Solution[a]	2003
Amoxicillin Powder, For Suspension[b]	2015
Amphetamine Aspartate Monohydrate, Amphetamine Sulfate, Dextroamphetamine Saccharate, Dextroamphetamine Sulfate Tablet[c]	current
Atropine Sulfate Injection[d]	current
Azacitidine Injection	2021
Bupivacaine Hydrochloride Injection[e]	2018
Bupivacaine Hydrochloride, Epinephrine Bitartrate Injection	2011
Cefotaxime Sodium Injection	2018
Dexamethasone Sodium Phosphate Injection	2018
Dexmedetomidine Hydrochloride Injection	2020
Dopamine Hydrochloride Injection[f]	2005
Epinephrine Injection, Syringes[f]	2020
Erythromycin Ointment	2011
Etomidate Injection	2011
Fentanyl Citrate Injection	2020
Furosemide Injection	2005
Heparin Sodium Injection	2012
Hydromorphone Hydrochloride Injection	2020
Ketamine Hydrochloride Injection	2023
Lidocaine Hydrochloride Injection	2020
Lidocaine Hydrochloride Solution	2020
Methotrexate Sodium Injection	2021
Midazolam Hydrochloride Injection	2018
Morphine Sulfate Injection	2020
Parathyroid Hormone Injection	2004
Penicillin G Benzathine Injection	2012
Promethazine Hydrochloride Injection	2011
Rocuronium Bromide Injection	2023
Ropivacaine Hydrochloride Injection	2020
Sodium Chloride 0.9% Injection[g]	2018
Sodium Chloride 0.9% Irrigation	2018
Sodium Phosphate, Dibasic, Anhydrous, Sodium Phosphate, Monobasic, Monohydrate Injection	2014
Sucralfate Tablet	2012
Sufentanil Citrate Injection[h]	2020
Technetium TC-99M Pyrophosphate Kit Injection[f]	2014

[a] Albuterol 90 µg CFC and HFA formulations; [b] Amoxicillin 400 MG/5 ML SUSP 100ML; [c] Dextroamphetamine/ Amphetamine; [d] Antidote treatment, nerve agent, Automatic, Dual-Chamber, Pralidoxime Chloride Injection, 300 mg per mL, 2 mL, and Atropine Injection, 2.99 mg per mL, 0.7 mL; [e] Bupivacaine .25% Plain 50Ml VI , 1, VI; [f] More recent contracts may exist but ambiguous descriptions of formulation mean this cannot be confirmed. This listing is the most direct description match; [g] Sodium Chloride .9% 100 ML, 96 in each case, NDC 00338004903 or Equal; [h] Sufentanil NanoTab. Intended for battlefield use.

1.3 At the same time, the Department of Defense is facing increases in prescription drug costs, which have outpaced inflation.

The 2023 Evaluation of the TRICARE Program found increases in overall per-capita prescription drug costs in every beneficiary group (Figure 4).[10] Annual increases in all groups outpaced inflation, by a margin ranging between +5% for retirees and family members aged 65 and older and +13% for active duty family members with a network primary care manager.[3] Average annual DOD prescription costs per beneficiary remained relatively steady 2020–2022 when delivered directly, but have increased in private-sector care covered by DOD.

Figure 4. Average Annual DoD Prescription Costs per Beneficiary, Fiscal Years 2020-2022.[3]



Source: MHS administrative data, 1/20/2023

[a] Excludes retail drug refunds.

[b] Direct care prescription costs include an MHS-derived dispensing fee.

Notes:

– The Retirees and Family Members groups include survivors and others not explicitly identified elsewhere.

– Numbers may not sum to bar totals due to rounding.

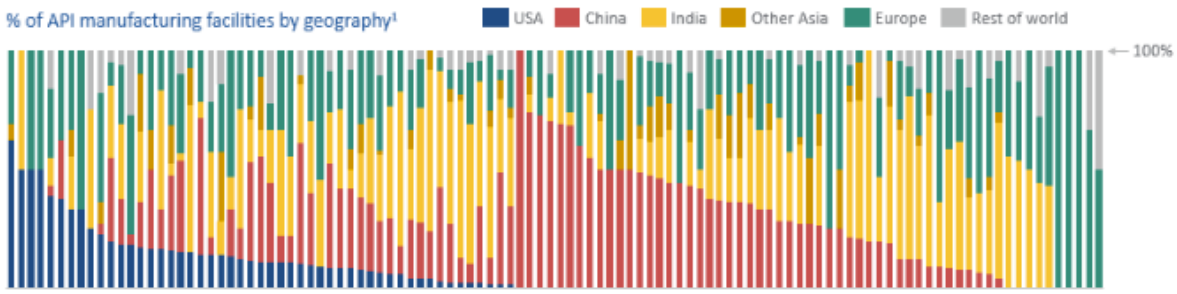
1.4 The increasing market concentration of key starting material (KSM) and active pharmaceutical ingredient (API) manufacturing is an important driver of shortages. Reversing this trend will require long-term strategies and investment to diversity supply and increase domestic capacity.

Some drugs are only manufactured by one or two suppliers, rendering them especially vulnerable to supply disruptions and/or demand shocks. A 2023 study in *Health Affairs* found that approximately one-third of generic APIs produced for use in the United States

market between 2020 and 2021 were manufactured by a single facility; an additional third was manufactured by two or three facilities.[11] The same study found that "23.0 percent of markets had upstream vulnerabilities to the supply chain because a robust level of competition among finished drug manufacturers obscured a fundamentally uncompetitive market of three or fewer API producers."[11]

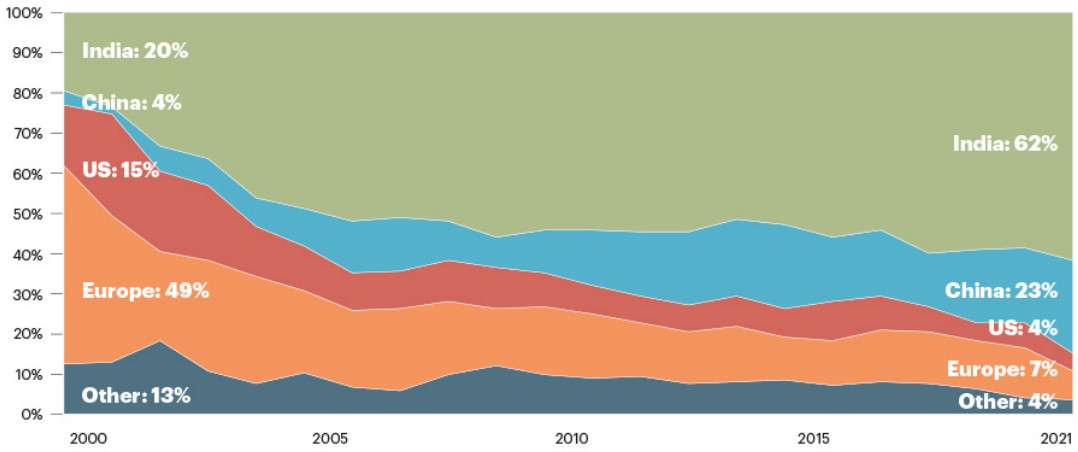
The Senate Committee on Homeland Security and Governmental Affairs issued a report in 2023 noting that "90 to 95 percent of generic sterile injectable drugs for critical acute care in the U.S. rely on key starting materials and drug substances from China and India."[7] The report concluded that "the lack of robust domestic manufacturing capacity and diversification of suppliers for critical generic drugs prone to shortage, leaves the U.S. vulnerable to a variety of threats."[7] Estimates of reliance on supply from China are likely underestimates, as they generally measure transfers of API, but exclude the chemicals used to manufacture API. There is no systematic monitoring of API transactions, but some have estimated that as much of 70% of India's API uses chemicals sourced from China.[3] Using commercial (Clarivate) data, the report documented that roughly half of 118 essential medicines (as defined by FDA) have domestic API manufacturing sites (Figure 5).[7]

Figure 5. Percentage of API Manufacturing Facilities by Geography for 118 Critical Medicines.[12]



India and China have increased their market share over 2000–2020 (Figure 5), with India now estimated to account for 62% of API drug master files and China 23%. In the same period, the number of API Drug Master Files attributed to US-based manufacturers has decreased from 15% to 4%, and the number of those attributed to Europe-based manufacturers, from 49% to 7%.

Figure 6. Active API Drug Master Files, by year of filing and country of manufacture[13]

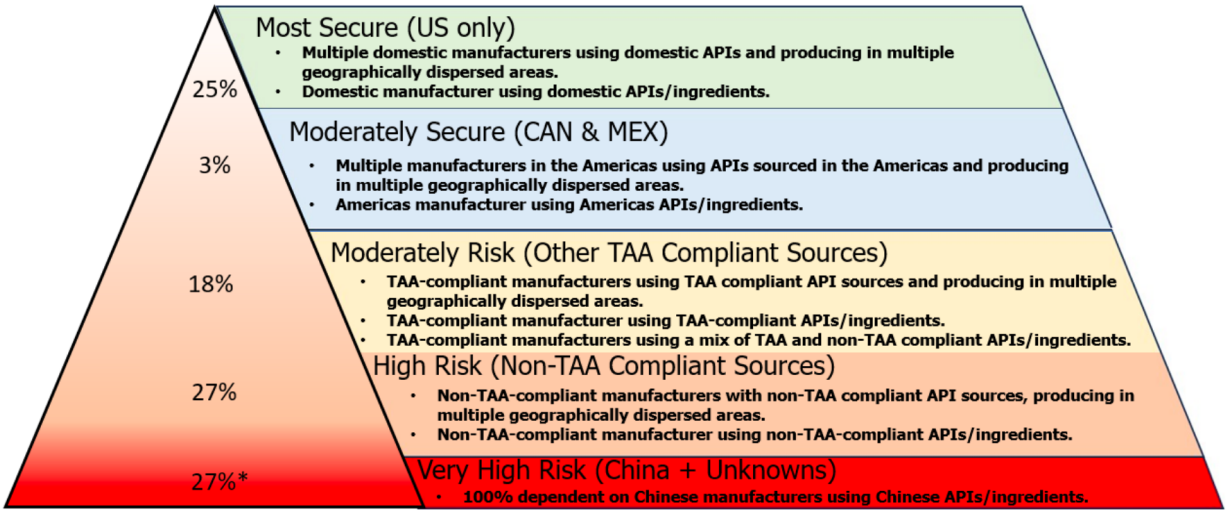


In testimony to the U.S.-China Economic and Security Review Commission hearing *Exploring the Growing U.S. Reliance on China's Biotech and Pharmaceutical Products,* Christopher Priest (Principal Deputy, Deputy Assistant Director of Healthcare Operations at the Defense Health Agency) described the strategic implications of gaps in API data, noting that "concerns about any situation where foreign actors, such as China, control substantial access to critical warfighting materiel and potential serious risk of interruptions in the supply chain or posed by contaminated APIs…is compounded by the fact that there is no required registry for API sources making it extremely difficult to gauge the extent of the risk."[6]

Recognizing the strategic and health importance of ensuring secure, diversified supply chains, the Office of the Under Secretary of Defense for Acquisition and Sustainment analyzed API sources of 12,917 drugs (10% of the US marketplace).[4] The report concluded that "DoD has a high dependence on foreign material and trade agreements to maintain current pharmaceutical capabilities" and characterized "54% of the DoD pharmaceutical supply chain [as] considered either high or very high risk, with dependency on non-Trade Agreements Act (TAA)[2] compliant suppliers, sourcing from China and India, or unknown."[4] A summary of the API risk assessment for the 12,917 drugs (10% of US commercial market) analyzed is reproduced as Figure 7.[4]

[2] The Office of the Under Secretary of Defense for Acquisition and Sustainment 2023 report defined TAA-compliant and TAA non-compliant as follows: "For the purposes of this report [2023 *Report on the Department of Defense Pharmaceutical Supply Chain Risks*], the term "TAA Compliant" means that the sources of both finished pharmaceuticals and APIs or key ingredients are U.S. -made or a qualifying country or designated country item API. The term "TAA Non-Compliant" for purposes of this report does not include application of the definition of U.S.-made end product as defined in Defense Federal Acquisition Regulation Supplement (DFARS) clause 252.225-7021. If the API or key ingredients have not been substantially transformed in the U.S., a qualifying country, or designated country, then the item is "TAA Non-compliant" for the purposes of this report."[4]

Figure 7. DLA hierarchy of drug security.[4]



Analyses of global API distribution and flows are impeded by data gaps. In some cases, multiple suppliers of a given final drug will use the same API supplier. This means that drugs that appear to have a robust multi-source supply chain may in fact be reliant, upstream, on one or a few API manufacturers and may thus be less resilient than is apparent. This structure also has the effect of obscuring the relative volumes and ultimate source for raw materials: approved drug applications must disclose the sources of supply, but FDA does not know whether supply is split evenly across facilities, or if, for example, one facility produces 99% of product while another produces just 1%.

In its analysis of DOD supply chains, DLA noted that even "with all its specialized expertise, available databases, and IT support tools and capabilities", they were unable to identify source of 22% of APIs.[4] Mending the deep cracks in the information ecology around API sourcing will require more than merely increasing required disclosure by manufacturers – these efforts, while important, at best only address drugs currently registered in the United States. Any risk mapping requires an understanding of API production globally, and will require investments in improving data collection to realize.

1.5 Increasing the prices paid for drugs is neither an efficient nor effective strategy to prevent future shortages, unless tied to conditionalities requiring manufacturers to demonstrate investments addressing the underlying causes of shortages (e.g., improving risk management practices, diversifying supply sources, investing in back-up manufacturing capabilities, and other reforms to improve supply chain robustness.)

Shortages for some medicines have been attributed by some to prices that are too low. Price is always a factor in questions of supply, and an FDA analysis on the "root cause of

shortages" estimated that half of the 163 drugs that went into shortage from 2013-2017 "may have had inadequate financial incentives to market the product or invest in ensuring manufacturing capability and capacity prior to the shortage."[14] However, studies of shortages of generic sterile injectables suggest that manufacturing issues, rather than price declines, are more predictive of shortages. Research undertaken by the FDA analyzing shortages found that supply disruptions for drugs in shortage persist even after some price increases.[14]

A 2016 analysis of shortages of sterile injectable drugs undertaken by the Government Accountability Office (GAO) concluded that the two most strongly predictive factors of shortages were a) a decline in the number of suppliers and b) the failure of at least one manufacturer to comply with manufacturing standards, resulting in an FDA warning letter. Sales of a generic version were also predictive, but price decline was not found to be statistically correlated with shortages of drugs in this study (See Table 3). The ongoing penicillin G benzathine shortage (see 1.3) also points to a more complex relationship between price and availability. According to the FDA, the drug has been in shortage since at least 2012. Since 2013, the price has increased 275% to $470 per 4 mL syringe.[8]

Table 3. Estimated Percentage Point Increase in Probability of a Drug Shortage in the Presence of Certain Factors, for Sterile Injectable Anti-infective and Cardiovascular Drugs, 2012-2014[15]

The estimated mean probability of a shortage predicted for all drugs in our study by the model is 60.7 percent.

Factors	Estimated percentage point increase in the probability of a shortage[a]
Decrease in suppliers, previous 2 years	16.8**
Sales of a generic version, previous year	12.3**
Failure to comply with manufacturing standards resulting in a warning letter, previous 2 years	8.1**
Price decline, previous 2 years	0.7

Source: GAO analysis of data from IMS Health, the Food and Drug Administration, and the University of Utah Drug Information Service | GAO-16-595.

Notes: Our multivariate logistic regression model uses a 3-year panel data file that contains shortage measures for 118 sterile injectable anti-infective and cardiovascular drugs from 2012 through 2014 and measures of market structure (whether there was a decrease in suppliers), compliance with FDA manufacturing standards (whether there was a failure to comply with manufacturing standards resulting in a warning letter for at least one establishment that manufactured the drug), drug characteristics (whether sales of a generic version), and price and volume of sales (whether the price declined) from 2010 through 2013.

[a]The estimated percentage point increase in the probability of a shortage is calculated as the difference between (1) the probability of a shortage if the factor is present for all drugs and the other three factors remain unchanged and (2) the mean probability of a shortage predicted for all drugs in our study by the model (60.7 percent). To compute the predicted probability of a shortage when the characteristic is present, we set the value of the variable to one, left the values of the other explanatory variables unchanged, and then calculated the probability using the coefficients estimated from our 3-year repeated measures logistic regression model. To compute the mean probability of a shortage predicted for all drugs in our study by the model, we first computed the predicted probability of a shortage for every drug and every year in our study by using the estimated coefficients from the model and the data for each drug. We then computed the mean of the 354 predicted values (118 drugs and 3 years), which was 0.607, or 60.7 percent.

** indicates that the estimated probability is based on a coefficient estimate that was significant at a level of 0.01 or better, based on our logistic regression model results.

2. Meeting defense health needs in a mixed economy: past lessons and future directions.

2.1 Public sector R&D has yielded breakthroughs of immense military (and wider public health) significance.

The military has developed health products for specific combat missions: the botulinum toxoid vaccine was developed for D-Day because of concerns regarding a bioweapon attack using the toxin, and the Japanese encephalitis vaccine was developed for an anticipated ground invasion of Japan.[4]

Still more important are military investments to research, develop, and manufacture health products for infectious diseases. Preventing infectious disease as a key defense priority predates the establishment of the United States: George Washington famously insisted that his army be variolated against smallpox.[16]

The 2023 Biodefense Posture Review emphasized the critical importance of health in defense strategy, noting that "the most likely infectious disease threats to deployed U.S. forces come from endemic diseases (i.e., diseases that regularly occur in a particular population or area). Respiratory diseases (e.g., tuberculosis, seasonal influenza), food and waterborne diseases (e.g., typhoid, cholera), and vector-borne diseases (e.g., malaria, dengue fever) may cause local or regional epidemics."[5]

Most of these diseases receive very limited private sector research and development (R&D) investments.[17] The private sector has not historically engaged in significant R&D for health conditions with limited commercial markets. Public investments and public labs have been instrumental in developing treatments and vaccines that have saved countless lives and improved military readiness. A summary of some of accomplishments in vaccine research was compiled in a 2002 report by the Institute of Medicine (IOM) of the National Academies (Appendix A).[8]

Penicillin, perhaps the most important therapeutic advance of the twentieth century, would have likely been delayed by years, if not decades, without public investments in improving manufacturing processes. Penicillin was discovered in 1928, but manufacturing technologies at the time could only produce minuscule supplies: supply was so scarce that penicillin was extracted from patients' urine and re-used.[18] The US Office of Scientific Research and Development's Committee on Medical Research (OSRD / CMR) and the U.S. Department of Agriculture's Northern Regional Research Laboratory (NRRL) played a key role in developing production processes that allowed the drug to be mass-produced, leading to sufficient quantities being available for routine military use by 1944.[19] OSRD was established

by FDR in 1941 to mobilize and coordinate research undertaken in both civilian and military spheres for defense purposes.[20]

The production technology used and improved through public research – a fermentation process – was considered by the private sector to be far more expensive than manufacture through chemical synthesis; commercial firms preferred to wait until synthesis became possible.[19] However, chemical synthesis of penicillin was not developed until 1959, and even then, was not as efficient as fermentation methods until 1992.[19] The case of penicillin highlights the perils of the military relying on commercial markets to meet defense needs: without public investments aimed at addressing military health needs, widespread availability of the antibiotic may have been delayed by almost three decades.

Maintaining readiness requires the development of vaccines and other products that prevent illness, not just treatments. For some diseases, the existence of a treatment has made markets for preventative products less attractive to the sector. One example is the pneumococcal capsular polysaccharide vaccine. Streptococcus pneumoniae (or 'pneumococcus') causes pneumonia and, less frequently, meningitis – both of which can be serious or fatal. Though prevention is always preferable to curing disease after infection, private sector interest in developing a vaccine dissipated after an effective treatment (sulphonamide antibiotics) was discovered. Respiratory diseases are easily transmitted in military barracks, resulting in antibiotic use that exceeds typical civilian use. By 1944 antibiotic resistance was observed at a Sioux Falls, South Dakota Air Force base.[21] Because sulphonamides were generally still effective in the wider population, military needs for a vaccine preceded the market sizes that might have incentivized the private sector to engage in R&D.[21] As noted by Hoyt, "[a]ll efforts to develop a new vaccine to induce active immunity would likely have come to a halt if the military did not have an enduring interest in population-based preventive measures."[21] The Board for the Investigation and Control of Influenza and other Epidemic Diseases (BICIED, later renamed the Army Epidemiology Board) carried out research and identified the most common pneumococcus strains prevalent among military personnel, allowing the development of a vaccine, with confirmatory clinical testing conducted by the US Army Medical corps.[21]

The military has also undertaken R&D to improve upon products offered by the private sector. Improvements to the tetanus vaccine are the result of the Army finding that earlier tetanus vaccinations caused a high number of adverse effects.[21] Research by the Preventive Medicine Division identified a key driver of these adverse effects (peptones in the nutrient media used to grow the bacteria), and an improved vaccine without these side effects was developed.[21]

2.2 However, the public sector does not just undertake R&D: there is a long history of the public sector also stepping in to manufacture drugs for military use.

The often-cited 'division of labor' between the public and private sectors, wherein the public sector undertakes R&D through national labs like Walter Reed Army Institute of Research (WRAIR) and the National Institutes of Health (NIH), and the private sector takes over manufacturing, were the result of policy choices rather than any intrinsic necessity. The division largely dates to the aftermath of WWII, when the Secretary of War directed that military production be shifted "to the maximum practicable extent" to the private sector.[21] However, this division was not absolute, and the public sector has continued to be, in some cases, the only manufacturer of key health technologies. The cases below – while far from comprehensive – highlight government-owned, government operated (GOGO) and/or government-owned, contractor-operated (GOCO) initiatives for health product manufacturing that have played an important role in US military history.

US Civil War: The first industrial-scale manufacturing of medicines by the United States military of which I am aware occurred during the Civil War. Reliable access to medicines was decisive in some battles: historians attribute the failure of the first siege of Vicksburg to shortages of quinine, a medicine used for malaria prevention.[22,23] The military investigated the cost of production of some needed medicines and found that in-house manufacturing would likely be cost effective.[1] Subsequently, the US Army invested $200,000 (about $6 million in 2024 dollars) in setting up facilities for government manufacture of medicines in Astoria and Philadelphia.[1] In terms of governance, these facilities were operated out of the military Medical and Hospital Department funds rather than the War Office.[1] Eventually these early GOGO facilities would manufacture more than 100 different tinctures, extracts, powders, and pills.[24] Reviews of the initiative found that the drugs they produced were of good quality, and that the effort was important in stabilizing supply.[1]

In addition to stabilizing supply chains – a key defense priority – the establishment of manufacturing facilities had a secondary consequence of substantial cost savings.

First, savings were achieved through decreased direct expenditures. Even accounting for capital investments and start-up costs, the Philadelphia facility alone was estimated to have saved the US government $766,019 ($24 million in 2024 dollars).[25]

Second, government facilities indirectly reduced overall expenditures by curbing the worst excesses of firms abusing their dominant market position to increase drug prices. Quinine was of especial strategic importance, as malaria was endemic in many spheres of battle. Military purchasers contended with sharp price increases: quinine prices increased by seventy percent, from $2.10 per ounce in 1861 to $3.60 in 1863 ($89 in 2024 dollars).[1] These price increases were the result of abuse of market power, rather than an increase in the cost of

doing business, with the New York Times reporting that "[quinine] is speculated in, in the same manner as Gold."[26] The mere announcement of the government's intention to manufacture its own quinine resulted in price decreases of more than thirty percent in a single day, and by the end of the week, private manufacturers were offering $0.70 discounts.[26]

WWII: Penicillin was discovered in 1928, but insufficient quantities were able to be produced with existing technologies (see 2.1). The US Office of Scientific Research and Development's Committee on Medical Research (OSRD / CMR) and the U.S. Department of Agriculture's Northern Regional Research Laboratory (NRRL) played a key role in developing production processes that allowed the drug to be mass-produced for military use. But the public's role was not restricted to R&D: the War Production Board also constructed penicillin production facilities.[19]

The US Army Medical Department also identified dengue serotypes in response to high (up to 12%) infection rates among troops stationed in Melanesia during WWII,[27,28] and the Walter Reed Army Institute of Research (WRAIR) later developed a live-attenuated, tetravalent dengue virus vaccine candidate, which was manufactured at the WRAIR Pilot Bioproduction Facility.[28]

MassBiologics: In the mid-1930s-40s, MassBiologics (at this time, "the State Biologic Laboratories"), Harvard Medical School, the U.S. Navy, and the American Red Cross collaborated to extract and distribute over 10,000 grams of gamma-globulin antibodies to address the measles outbreaks.[29] The Laboratories signed a contract with the U.S. Navy to bring nearly 2 million doses of the antibody to soldiers and the public.[29] Produced between 1934-1944, these measles antibodies were the first human blood-derived products to be distributed by the Biologic Laboratories.[29]

Michigan Department of Health: The Michigan State Department of Health manufactured the anthrax vaccine for the Pentagon from 1964 to 1995.[34] The US Army provided necessary expertise and equipment to the Michigan State Department of Health to develop and produce the anthrax vaccine to serve DoD requirements.[34]

2.3 Contractor-owned, contractor operated (COCO) facilities have sometime been characterized as cost-saving and lower risk compared to government-owned, contractor-operated (GOCO) or government-owned, government operated (GOGO) alternatives. However, COCO models have not always resulted in the desired efficiencies, and have in some cases resulted in preventable morbidity and mortality among people serving in the military.

Policy efforts to encourage the private sector to engage in markets serving military needs have been unsuccessful in certain key areas. In 1991, the GAO (then named General Accounting Office) conducted a review analyzing whether the Army's only option for developing and producing needed vaccines was with the non-profit Salk Institute, or if there were opportunities for greater private sector involvement. After speaking with several commercial vaccine manufacturers, the GAO concluded that there was no commercial market.[35] More recently, in 2021, a GAO (now the Government Accountability Office) study found that the "lack of [domestic] surge capacity is caused partially by the reluctance of vaccine manufacturers in the private sector to invest in the high cost of maintaining excess, idle capacity in anticipation of unknown future vaccine."[36]

The cases of the anthrax, plague, and adenovirus vaccines offer illustrative examples of the risks of a lack of public oversight and control over the production and control of drugs essential for military use.

Anthrax: The Michigan State Department of Health was the sole manufacturer of the anthrax vaccine for the Pentagon during 1964–1995 (see 2.3).[34] The facility and license to manufacture the anthrax vaccine was transferred from public ownership to BioPort Corporation for $25 million in 1998. This transfer was done with significant underwriting of risk by the public sector: BioPort only paid $3.3 million in cash, and the state of Michigan provided the rest of the $25 million in financing.[37] BioPort was then in turn provided $15 million for capital investments to expand production and over $60 million in Pentagon contracts to continue providing needed anthrax vaccines.[38] DOD also agreed to pay up to 75% of the cost of the vaccine, whether or not BioPort succeeded in securing a license for use.[37]

One year later, BioPort increased the price per dose agreed at the time of the sale from $4.36/dose to $10.64/dose.[39] The Defense Contract Auditing Agency (DCAA) found BioPort's price increase to be "overstated" and recommended that accounts be carefully reviewed before any price increases were approved.[40] A report issued by the Committee on Government Reform described BioPort as "not [to] be a reliable financial partner in the vaccine enterprise."[41] An expert witness testifying in a 2004 hearing of the Select Committee on Homeland Security described DOD's position as one wherein "threats to stop production render[ed] DOD unable to resist demands for extraordinary financial relief and pressure to permit the use of publicly funded improvements to monopolize the private domestic and foreign markets as well."[42]

Despite significant investments from the Pentagon, BioPort was unable to produce any vaccine for four years, and failed FDA inspections during the first 2 years of operation.[38,43] In reviewing the supply challenges, GAO concluded that "if we are relying upon this vaccine as part of the backbone of our defensive biological program, the question of vulnerability to

a single site becomes an issue."[44] BioPort's record was described in a 2000 Senate Armed Services Committee hearing as "an unmitigated disaster… costing the American taxpayer millions and millions of dollars and jeopardizing the safety of our troops who we're not able to provide that anthrax vaccination."[38]

Adenovirus: An adenovirus vaccine was developed by the military (see Appendix A), but the sole manufacturer was Wyeth Laboratories. In 1996, Wyeth Laboratories requested funding from the Pentagon to make facility improvements.[45] Wyeth refused to invest in the facility themselves, and wound down adenovirus production. No other private sector manufacturer filled the gap, and supply ran out by 1999.[45]

Without vaccination, "adenovirus illness reemerged as a major cause of illness and hospitalization among new trainees" by 2002.[46] Medical services were interrupted, with at least three basic training facilities becoming overwhelmed after outbreaks, resulting in medical staffing challenges and requiring some bases to convert barracks to infirmaries.[46] At least two recruits died.[46] The number of recruits having to repeat basic training due to days lost to illness increased by as much as 20-fold.[46] It took 10 years and $100 million for DOD to be able to re-introduce adenovirus vaccination among military trainees.[47] Cost-effectiveness analysis undertaken in 1998 estimated that without vaccination, adenoviral acute respiratory disease (ARD) outbreaks resulted in over twelve thousand cases of ARD hospitalization and cost the Army $26.4 million.[48]

Plague: Greer Laboratories, the only manufacturer of the plague vaccine, received a warning letter from the FDA, and subsequently the business decision was made to discontinue the vaccine in 1998. No private sector provider was found, and to date there is no licensed vaccine available.[46,49]

2.4. Government-owned, government operated (GOGO) and/or Government-owned, Contractor-operated (GOCO) facilities have been recommended for decades as a solution to DOD supply challenges and pursued on a bipartisan basis. DOD should act on these recommendations and establish a GOGO facility for priority health products. Such a facility would ensure reliable access to quality drugs to meet DOD needs, as well as generate significant cost savings.

GOGO and GOCO models have been successful in ensuring reliable access to drugs on a cost-effective basis (Sections 2.1 – 2.2). A range of government reviews in recent decades have recommended GOGO and GOCO models to address military drug production needs.

The DOD commissioned a special task force ("Project Badger") in the 1990s to assess whether or not commercial markets could serve defense needs.[42] After making inquiries to all commercial manufacturers as to their interest and ability to manufacture needed vaccines,

the task force concluded that "the best option appeared to be a facility that was government owned (and funded)."[42] The proposed model was a government-owned, contractor-operated (GOCO) model, where the government would own and construct a facility as a "national asset", but a contractor would staff production.[42] In the mid-1990s, a GOCO vaccine facility was included within a DOD budget request but "was subsequently withdrawn in favor of an approach that relies upon private industry to meet the vaccine needs of the DOD." [42]

Separately, a GAO report recommended in 1991 that "the Army could improve and expand its in-house vaccine production facilities to meet its needs."[35]. Walter Reed Army Institute of Research (WRAIR), laboratory suites at the Medical Research Institute of Infectious Diseases at Fort Detrick, and an NIH-owned GOCO facility were proposed as possible sites.[35] A pilot program was proposed, but by 1994 an amendment was introduced to specifically prohibit DoD from further pursuing this initiative.[50]

In 2000, the Institute of Medicine (IOM) of the National Academies convened an expert committee to advise the U.S. Army Medical Research and Materiel Command on production, with a focus on the "naturally occurring disease threats" that are a priority of DHA. The resulting 2002 Expert Committee report recommended that DOD pursue GOCO production facilities.

GOCO initiatives have attracted bipartisan legislative support. Former Republican Governor Jim Gilmore, head of the 2001 Advisory Panel to Assess Domestic Response Capabilities for Terrorism" argued that "The establishment of a government-owned, contractor-operated national facility for the research, development and production of vaccines and therapeutics for specified infectious, especially contagious diseases, is needed."[51]

The *New York Times* reported plans by the Pentagon to "[build] its own vaccine plant to produce eight vaccines for military use – the existing anthrax vaccine and a new one, plus vaccines for smallpox, plague, tularemia, botulinum, ricin and equine encephalitis. It would cost $1.56 billion to build and run over 25 years, including $386 million in construction costs, the department estimated."[45] Further details of the proposed program are either not in the public domain or I was unable to locate them.

As part of the 2003 National Defense Authorization Act, a bipartisan amendment was introduced by Senator Hutchison of Texas (R), Senator Mikulski of Maryland (D), Senator Lincoln of Arkansas (D), Senator Sarbanes of Maryland (D), and Senator Roberts of Kansas (R) authorizing the construction of a "government-owned, contractor operated facility" for the "production of vaccines for agents known or anticipated to be used in biological weapons", for which "The Secretary shall provide for the operation of the facility constructed … as a government-owned, contractor-operated facility."[52] In introducing the

amendment, the sponsor Senator Hutchinson (R-AR) defended the importance of the public sector in provision of some essential medical goods:

> *"This problem has been examined many times over the past decade. In fact, it has been studied twice by the Department of Defense. Both times, the conclusion was that our Nation needed a government-owned, contractor-operated vaccine production facility…The private sector, for all of the good that it does, cannot, against some of the boutique biological pathogens and threats that may exist now and in the future against our troops and against our civilian population, and will not in the future see this as a profitable commercial venture. The insurance for the American people, and the insurance for our men and women in uniform, is to have a Government-owned production facility, contractor-operated, to ensure that vaccine will always be available if and when it is needed."* [51]

In a 2004 hearing of the Select Committee on Homeland Security, committee members and expert witnesses discussed the (by that time de-classified) Project Badger findings in the context of revived proposal to establish a GOCO to serve defense medical needs.[42] Major General Lester Martinez-Lopez (Commanding General, U.S. Army Medical Research and Materiel Command, Fort Detrick, Maryland) described the benefits of government owned facilities as "government control of production, availability, and distribution flexibility for emergency production technologies meets national security priorities for bio-defense vaccines overcomes limited industry interest in bio-defense products."[42]

Another expert witness – an experienced researcher and administrator of biological defense programs – acknowledged the political challenge of introducing the GOCO model. Reflecting on the urgent need and failure of the COCO model to deliver reliable access to needed drugs, she strongly encouraged the Select Committee to support the GOCO proposal:

> *"Although the pharmaceutical firms seem opposed to the GOCO approach, citing the availability of capacity already existing, this belies that fact that each year industry has difficulty meeting existing market demands. Recent shortages in tetanus, pertussis, and flu vaccines support the perception that there is no excess capacity available for biodefense vaccine work… As time passes, the costs [of building government-owned facilities] will only increase, and the nation will be at the mercy of the fragile, profit-motivated pharmaceutical industry to make the bio-defense vaccines that are needed. In my opinion, Congress should strongly consider appropriating funds for a GOCO facility for bio-defense medical countermeasures.*[42]

The hearing also highlighted operational and strategic advantages of GOGO and GOCO models over COCO models, including: [42]

- RFPs are not required for each product
- Long-term contracts a) provide needed stability in small markets; b) encourage increased capacity by operating contractors for specialized production needs and

regulatory requirements; c) signal sustained government support for medical countermeasures

- Increased efficiencies and flexibility as production needs can be decided by the government on an as-needed basis
- Bidirectional efficiencies and opportunities for innovation through collaborations with government R&D labs

A key theme in the 2023 DOD Biodefense Posture Review was the need for an integrated approach by the Chemical and Biological Defense Program (CBDP) and Defense Health Program (DHP). The Review recommended that DOD "review DHP and DHA efforts to enable far-forward care, speed clinical trials and research within the Military Health System, inform optimal clinical care strategies, and support development of MCM specific to the military population." The BDP ultimately concluded that the "CBDP and DHP have sufficiently unique missions, partners, and processes that drive a "spirit of competition" and innovation that argue against consolidating authorities and responsibilities into a single program."

A second key theme in the Biodefense Posture Review was the importance of ensuring supply chain reliability for key medical products. The Review recommended that the Chemical and Biological Defense Program (CBDP) and Defense Health Program (DHP) should partner with the Office of the Assistant Secretary of Defense for Industrial Base Policy "to prioritize on-shoring of production and distribution of key chemicals critical to produce DoD-unique biodefense MCMs." The Review recommended use of the Defense Production Act (DPA) and Manufacturing Innovation Institutes to expand domestic API production.

2.5 Congress should consider introducing legislation establishing clear options for creating a government-owned facility to manufacture priority health products to meet DOD needs. Such a facility would ensure reliable access to quality drugs for servicemembers, as well as generate significant cost savings.

Maintaining access to quality health products for servicemembers is a critical part of defense strategy. Manufacturing drugs for military use is not a new idea: GOGOs for pharmaceutical production stretch back to at least the Civil War, and analyses by government agencies have recommended GOGOs and GOCOs as a solution to persistent supply challenges for decades.

At present, government creation of manufacturing capacity is often done in a reactive manner, with initiatives created (after a delay) in response to particular crises. Congress should consider introducing legislation establishing clear options for creating a government-

owned facility to manufacture priority health products to meet DOD needs. To avoid the delays and added administrative overhead in this reactive approach, a streamlined and regularized mechanism for identifying relevant needs and feasibility could be created. Such a facility would ensure reliable access to quality drugs for servicemembers, as well as generate significant cost savings.

Appendix A

Table A1. Historical Highlights in the Control of U.S. Military Infectious Diseases by Vaccines[46,53]

1777	Members of Continental Army inoculated with the variola virus to prevent smallpox
1812	Cowpox immunization replaced variolation for prevention of smallpox in troops
1909	Typhoid vaccine developed
1927	Chloroform-treated single-dose rabies vaccine for dogs developed through work done in the Philippines
1940s	Dengue virus types 1 and 2 isolated; first experiments begun with dengue vaccine
1940s	Tetanus toxoid and diphtheria toxoid shown to be highly effective in preventing wound-induced tetanus and diphtheria infections
1941	Armed Forces Epidemiological Board established; commissions established to deal with influenza, hepatitis, encephalitis, and other diseases that threatened the war effort; vaccine-related activities included conducting research and providing immunization policy advice
1942	Influenza vaccine developed and used for mass immunization of military forces
1942	Yellow fever vaccine used in large numbers of military personnel; hepatitis B virus contamination of serum causes a large common-source outbreak of jaundice
1944	Smallpox vaccine licensed
1944	Troops stationed in Okinawa, Japan, immunized against Japanese encephalitis
1950s	Discovery that adenovirus types 3, 4, and 7 cause most cases of acute respiratory diseases in recruits; adenovirus vaccine research and development initiated
1950s	Anthrax vaccine developed
1960s	Outbreaks of meningococcal meningitis on military posts stimulated the study of meningococcal infection and the development of vaccines against meningococcal groups A, C, Y, and W-135
1960s	Plague vaccine proven effective in Vietnam
1960s	Malaria vaccine program initiated (protection from bite of radiated mosquitoes shown)
1965–1969	INDs* filed for vaccines against Venezuelan equine encephalitis, tularemia, eastern equine encephalitis, and Rift Valley fever
1970s	Development and testing of an oral typhoid vaccine
1970s	Prototype vaccines against Russian spring-summer encephalitis and tick-borne encephalitis made at Walter Reed Army Institute of Research (WRAIR)
1970s	Live attenuated dengue virus vaccine strains developed; INDs filed
1970	Anthrax vaccine licensed
1972–1975	INDs filed for Q fever vaccine and live attenuated Venezuelan equine encephalitis virus vaccine

1980	Adenovirus vaccines licensed for use in military populations, leading to nearly complete control of epidemic respiratory diseases in recruits
1984–1986	INDs filed for vaccines against western equine encephalitis, Argentine hemorrhagic fever, Venezuelan equine encephalitis, and chikungunya virus
1985	Efficacy of Japanese encephalitis vaccine demonstrated in Thailand; licensure application coordinated by U.S. Army Medical Materiel Development Activity; license granted by Food and Drug Administration
1985–1986	Hepatitis A vaccine developed and tested by WRAIR
1986	WRAIR classification of human immunodeficiency virus infections published
1987	Manufacturing technology for hepatitis A vaccine transferred from WRAIR to a commercial manufacturer; vaccine licensed in 1995
1991	IND filed for Rift Valley fever vaccine
1996	Recombinant circumsporozoite malaria vaccine developed by the U.S. Army and an industrial partner shown to be protective in human volunteers
1997	First successful vaccine against Shigella developed, produced, and tested
1998	First DNA vaccine against malaria administered to humans

Table reproduced from: National Academies of Sciences, Engineering, and Medicine. 2002. *Protecting Our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military*. Washington, DC: The National Academies Press. [39,43] The NAM report adapted a table from Hoke CH Jr. 2000. *Military Infectious Diseases Research Program Background*. Presented at the First Meeting of the Institute of Medicine Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military, Washington, DC

Acknowledgements:

Given overlapping subject matter, some of the analysis of shortages in Section 1 is borrowed from written testimony I submitted to a U.S. House of Representatives Committee on Energy and Commerce, Subcommittee on Health hearing on shortages held in September 2023.

I am grateful to Amy Kapczysnki and Reshma Ramachandran for foundational work in conceptualizing and helping develop a set of research questions around the role of the public sector in the provision of essential health products. Assembling the dispersed literature on government investments in health product manufacturing is an enormous and yet incomplete task. I thank Sahil Agrawal, Laura Hallas, Trudel Pare, Athena Sofides, and Dolma Tsering for research support this year.

References

1. George Winston Smith. Medicines for the Union Army: The United States Army Laboratories During the Civil War. Madison, WS: American Institute of the History of Pharmacy; 1962.

2. Center for Drug Evaluation and Research. Current Drug Shortages [Internet]. U.S. Food and Drug Administration. [cited 2024 Apr 2];Available from: https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages

3. Building resilient supply chains, revitalizing American manufacturing, and fostering broad based growth: 100 day Reviews under Executive Order 12017 [Internet]. Washington, D.C., USA: The White House; 2021. Available from: https://www.whitehouse.gov/wp-content/uploads/2021/06/100-day-supply-chain-review-report.pdf

4. Office of the Under Secretary of Defense for Acquisition and Sustainment. Report on the Department of Defense Pharmaceutical Supply Chain Risks [Internet]. Washington, D.C., USA: 2023. Available from: https://www.warren.senate.gov/imo/media/doc/FY23%20NDAA%20sec%20860%20Risk%20management%20for%20DoD%20Pharmceuticals1.pdf

5. Biodefense Posture Review. Washington, D.C., USA: Department of Defense; 2023.

6. Exploring the Growing U.S. Reliance on China's Biotech and Pharmaceutical Products [Internet]. 2019;Available from: https://www.uscc.gov/sites/default/files/Priest%20US-China%20Commission%20Statement.pdf

7. United States Committee on Homeland Security & Governmental Affairs. Short supply: the health and national security risks of drug shortages [Internet]. Washington, D.C.: 2023. Available from: https://www.hsgac.senate.gov/wp-content/uploads/2023-06-06-HSGAC-Majority-Draft-Drug-Shortages-Report.-FINAL-CORRECTED.pdf

8. Benjamin Ryan. Antibiotic Shortage Could Worsen Syphilis Epidemic [Internet]. The New York Times. 2023;Available from: https://www.nytimes.com/2023/07/07/health/syphilis-epidemic-antibiotic-shortage-pfizer.html

9. TRICARE Formulary [Internet]. Health.mil. Available from: https://health.mil/Military-Health-Topics/Access-Cost-Quality-and-Safety/Pharmacy-Operations/TRICARE-Formulary?type=All

10. Defense Health Agency. Evaluation of the TRICARE Program: Fiscal Year 2023 Report to Congress. 2023;Available from: https://health.mil/Reference-Center/Reports/2023/09/07/Annual-Evaluation-of-TRICARE

11. Socal MP, Ahn K, Greene JA, Anderson GF. Competition And Vulnerabilities In The Global Supply Chain For US Generic Active Pharmaceutical Ingredients: Study examines the competition and vulnerabilities in the global supply chain for US generic active pharmaceutical ingredients. Health Affairs 2023;10–1377.

12. Newport Sourcing API Manufacturing Locations, Clarivate Analytics 2020. [Internet]. In: Building resilient supply chains, revitalizing American manufacturing, and fostering broad based growth: 100 day Reviews under Executive Order 12017. Washington, D.C., USA: 2021. Available from: https://www.whitehouse.gov/wp-content/uploads/2021/06/100-day-supply-chain-review-report.pdf

13. Geographic concentration of pharmaceuticalmanufacturing: USP Medicine Supply Map analysis [Internet]. US Pharmacopeia. 2022;Available from: https://qualitymatters.usp.org/geographic-concentration-pharmaceutical-manufacturing

14. USFDA. Drug Shortages: Root Causes and Potential Solutions [Internet]. 2023;Available from: https://www.fda.gov/media/131130/download?attachment

15. Government Accountability Office. Drug shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge [Internet]. Washington, D.C., USA: 2016. Available from: https://www.gao.gov/assets/gao-16-595.pdf.

16. Hoyt K. Long shot: vaccines for national defense. Cambridge, Mass: Harvard University Press; 2011.

17. Policy Cures Research. Neglected disease research and development: the status quo won't get us there [Internet]. Available from: https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2023/02/09104948/2022-G-FINDER-Neglected-Disease-report.pdf

18. Clark R. The life of Ernst Chain: penicillin and beyond [Internet]. New York, USA: St. Martin's Press; 2011.

19. Neushul P. Science, Government and the Mass Production of Penicillin. J Hist Med Allied Sci [Internet] 1993 [cited 2024 Jan 12];48(4):371–95. Available from: https://academic.oup.com/jhmas/article-lookup/doi/10.1093/jhmas/48.4.371

20. Executive Order 8807—Establishing the Office of Scientific Research and Development in the Executive Office of the President and Defining Its Functions and Duties.

21. Kendall Hoyt. Memorandum by the secretary of war to the chief of staff, "Research and Development in Biological Warfare" (September 13, 1945), NA: RG 165, E. 488, B. 182. In: Long shot: vaccines for National Defense. Cambridge, MA: Harvard University Press; 2012.

22. Freemon FR. Gangrene and glory: Medical care during the American Civil War [Internet]. University of Illinois Press; 2001.

23. Steiner PE. Disease in the Civil War: natural biological warfare in 1861-1865. CC Thomas; 1968.

24. Glenna R. Schroeder-Lein. The Encyclopedia of Civil War Medicine. Armonk, New York: M.E. Sharpe; 2008.

25. Flannery M. Civil War pharmacy: A history of drugs, drug supply and provision, and therapeutics for the Union and Confederacy [Internet]. CRC Press; 2004.

26. QUININE [Internet]. The New York Times. 1863;Available from: https://www.nytimes.com/1863/03/26/archives/news-from-washington-where-the-first-draft-is-to-be-made-what-is-to.html

27. Robert V. Gibbons, Matthew Streitz, Tatyana Babina, Jessica R. Fried. Dengue and US Military Operations from Spanish–American War through Today. Emerging Infectious Diseases [Internet] 2012;Available from: https://wwwnc.cdc.gov/eid/article/18/4/11-0134_article

28. Pintado Silva J, Fernandez-Sesma A. Challenges on the development of a dengue vaccine: a comprehensive review of the state of the art. J Gen Virol [Internet] 2023 [cited 2024 Apr 14];104(3):001831. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10228381/

29. Cohn EJ. The University and the Biologic Laboratories of the State of Massachusetts: A Short History. Harvard Medical Alumni Bulletin [Internet] 1950;24(3):75–9. Available from: https://archive.org/details/harvardmedical24harv/page/n3/mode/2up

30. MassBiologics research into preventive shot for Lyme disease continues to move forward [Internet]. Mass Chan Medical School. Available from: https://www.umassmed.edu/news/news-archives/2022/05/massbiologics-research-into-preventive-shot-for-lyme-disease-continues-to-move-forward/

31. Willey S. MassBiologics research into preventive shot for Lyme disease continues to move forward [Internet]. UMass Chan Medical School News. 2022 [cited 2023 Dec 11];Available from: https://www.umassmed.edu/news/news-archives/2022/05/massbiologics-research-into-preventive-shot-for-lyme-disease-continues-to-move-forward/

32. nonGMP Monoclonal Antibody / Protein Production [Internet]. Mass Chan Medical School. Available from: https://www.umassmed.edu/massbiologics/services/developmentservices/nongmpmonoclonalantibodyproduction/

33. A New Affiliation: the UMass Chan Medical School [Internet]. Mass Chan Medical School. Available from: https://www.umassmed.edu/massbiologics/history/history/a-new-affiliation-the-university-of-massachusetts-medical-school/

34. Nicholas Wade. A Vaccine That Experts Say Is Effective [Internet]. The New York Times. 1997;Available from: https://www.nytimes.com/1997/12/16/us/a-vaccine-that-experts-say-is-effective.html

35. General Accounting Office. Biological Warfare: Role of Salk Institute in Army's Research Program [Internet]. 1991;Available from: Washington, D.C., USA

36. Government Accountability Office. Technology Assessment: Vaccine Development Capabilities and Challenges for Addressing Infectious Diseases. Washington, D.C., USA: 2021.

37. Weiss MM, Weiss PD, Weiss JB. Anthrax Vaccine and Public Health Policy. American Journal of Public Health [Internet] 2007 [cited 2024 Apr 14];97(11):1945. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2040369/

38. Judith Miller. Company Led by Top Admiral Buys Michigan Vaccine Lab [Internet]. The New York Times. 1998;Available from: https://www.nytimes.com/1998/07/08/us/company-led-by-top-admiral-buys-michigan-vaccine-lab.html

39. Steven Lee Myers. U.S. Doubles Payment to Sole Source of Anthrax Vaccine [Internet]. The New York Times. 1999;Available from: https://www.nytimes.com/1999/08/06/us/us-doubles-payment-to-sole-source-of-anthrax-vaccine.html

40. General Accounting Office. Contract Management: Observations on DOD's Financial Relationship With the Anthrax Vaccine Manufacturer. Statement of Louis J. Rodrigues, Director, Defense Acquisitions Issues, National Security and International Affairs Division. Washington, D.C., USA: 1999.

41. The Department of Defense Anthrax Vaccine Immunization Program: Unproven Force Protection. Fourth report by the Committee on Government Reform together with dissenting and supplemental views [Internet]. 2000. Available from: https://www.congress.gov/congressional-report/106th-congress/house-report/556/1?q=%7B%22search%22%3A%22%5C%22Department+of+Defense+Anthrax+Vaccine+Immunization+Program%5C%22%22%7D&s=8&r=4

42. Towards a national biodefense strategy [Internet]. 2004;Available from: https://www.congress.gov/event/108th-congress/house-event/LC13942/text?s=1&r=61

43. Associated Press. A NATION CHALLENGED: THE VACCINE MAKER; Troubled Company Is Allowed To Resume Making Vaccine [Internet]. The New York Times. 2002;Available from: https://www.nytimes.com/2002/02/01/us/nation-challenged-vaccine-maker-troubled-company-allowed-resume-making-vaccine.html

44. Testimony of Louis J. Rodrigues, Director, Defense Acquisition Issues, National Security and International Relations Division, GAO, NSVAIR anthrax hearing (III). [Internet]. 2000. Available from: https://www.congress.gov/congressional-report/106th-congress/house-report/556/1?q=%7B%22search%22%3A%22%5C%22Department+of+Defense+Anthrax+Vaccine+Immunization+Program%5C%22%22%7D&s=8&r=4

45. Melody Petersen, Andrew Pollack. A NATION CHALLENGED: THE DEFENSES; Big Push to Accelerate Vaccine Effort [Internet]. The New York Times. 2001;Available from: https://www.nytimes.com/2001/09/28/business/a-nation-challenged-the-defenses-big-push-to-accelerate-vaccine-effort.html

46. Protecting Our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military [Internet]. Washington, D.C.: National Academies Press; 2002 [cited 2024 Apr 6]. Available from: http://www.nap.edu/catalog/10483

47. Hoke CH, Snyder CE. History of the restoration of adenovirus type 4 and type 7 vaccine, live oral (Adenovirus Vaccine) in the context of the Department of Defense acquisition system. Vaccine [Internet] 2013 [cited 2024 Apr 6];31(12):1623–32. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0264410X12017999

48. Howell MR, Nang MRN, Gaydos CA, Gaydos CJC. Prevention of Adenoviral Acute Respiratory Disease in Army Recruits:: Cost-Effectiveness of a Military Vaccination Policy 11The opinions presented are those of the authors and do not necessarily reflect the opinions of the Johns Hopkins University, the U.S. Department of Defense, or the U.S. Army. American Journal of Preventive Medicine [Internet] 1998 [cited 2024 Apr 14];14(3):168–75. Available from: https://www.sciencedirect.com/science/article/pii/S0749379797000640

49. Sun W, Singh AK. Plague vaccine: recent progress and prospects. npj Vaccines [Internet] 2019 [cited 2024 Apr 14];4(1):1–9. Available from: https://www.nature.com/articles/s41541-019-0105-9

50. Prohibition on use of funds for planning and design of Department of Defense vaccine production facility [Internet]. 1993. Available from: https://www.congress.gov/103/statute/STATUTE-107/STATUTE-107-Pg1547.pdf

51. Proceedings and Debates of the 107th Congress, Second Session. Congressional Record [Internet] 148(88). Available from: https://www.congress.gov/107/crec/2002/06/27/CREC-2002-06-27.pdf

52. Tim Hutchinson. S.Amdt.4069 to S.2514 [Internet]. Available from: https://www.congress.gov/amendment/107th-congress/senate-amendment/4069/text?s=1&r=77&q=%7B%22search%22%3A%22%26%231606%22%7D

53. Hoke CH Jr. Military Infectious Diseases Research Program Background. 2000.