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PERSONNEL AND READINESS

AUG 3 1 2023

The Honorable Mike D. Rodgers
Chairman
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

The Department's response to House Report 117–397, page 198, accompanying H.R. 7900, the National Defense Authorization Act for Fiscal Year 2023, "Novel Antibiotics Engineered to be Effective Against Drug Resistant Bacteria," is enclosed.

The report details the assessment of the Department of Defense's ability to prioritize procurement of novel antibiotics that have a demonstrated efficacy against multi-drug resistant bio-pathogens, the feasibility of prioritizing the procurement of novel antibiotics produced with domestically sourced ingredients and that are commercially available within the United States, and the feasibility of procuring and maintaining novel antibiotics to be held within the National Defense Stockpile.

Thank you for your continued strong support for the health and well-being of our Service members, veterans, and their families.

Sincerely,

[redacted]

Gilbert R. Cisneros, Jr.

Enclosure:
As stated

cc:
The Honorable Adam Smith
Ranking Member

Report to the Committee on Armed Services of the House of Representatives

Novel Antibiotics Engineered to be Effective Against Drug Resistant Bacteria

August 2023

The estimated cost of this report or study for the Department of Defense (DoD) is approximately $63,900 for the 2023 Fiscal Year. This includes $60,000 in expenses and $3,900 in DoD labor.

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A. CONGRESSIONAL REPORT REQUEST

This report is in response to House Report 117–397, page 198, accompanying H.R. 7900, the National Defense Authorization Act for Fiscal Year 2023, "Novel Antibiotics Engineered to be Effective Against Drug Resistant Bacteria," which requests that the Secretary of Defense (SecDef) assess and report on the ability of the Department of Defense (DoD) to prioritize manufacturing and procurement of domestically sourced novel antibiotics and ingredients required to produce such antibiotics.

House Report 117–397 requested that the report include the following:

1. An assessment of the DoD's ability to prioritize procurement of novel antibiotics that have a demonstrated efficacy against multi-drug resistant bio-pathogens and are consistent with the Food and Drug Administration (FDA) Drug and Biologics Essential Medicines, Medical Countermeasures, and Critical Inputs List.
2. The feasibility of prioritizing the procurement of novel antibiotics produced with domestically sourced ingredients and that are commercially available within the United States.
3. The feasibility of procuring and maintaining novel antibiotics to be held within the National Defense Stockpile.
4. Any statutory authority required for the Department to prioritize procurement of novel antibiotics produced from domestically sourced ingredients or to maintain a supply of such antibiotics.
5. Any other recommendations or data surrounding the procurement of novel antibiotics as determined by the SecDef.

B. PROCESS

A literature review was conducted to gather background information on each of the requested items included in House Report 117–397. Information and input were collected from relevant DoD Components.

C. FINDINGS: RESPONSES TO CONGRESSIONAL REQUIREMENTS

1. Prioritize Procurement of Novel Antibiotics

Request 1: An assessment of the Department's ability to prioritize procurement of novel antibiotics that have a demonstrated efficacy against multi-drug resistant bio-pathogens and are consistent with the FDA Drug and Biologics Essential Medicines, Medical Countermeasures, and Critical Inputs List.

While the DoD has not conducted a full assessment of the Department's ability to prioritize procurement of novel antibiotics consistent with the FDA Drug and Biologics Essential Medicines, Medical Countermeasures, and Critical Inputs List, multiple organizations within the Department have completed or have assessments underway. A full assessment of the ability to

prioritize procurement of novel antibiotics would include analysis of logistic, operational, and medically relevant factors.

Several factors impede DoD's ability for full control over supply and procurement systems for all critical needs to ensure capacity is available, accessible, and affordable. Four antibiotics on the FDA Essential Medicines list, for example, are in chronic short supply including amoxicillin, amphotericin B, clindamycin, and rifampin, making procurement of these drugs difficult. Furthermore, the Department of Health and Human Services Biomedical Advanced Research and Development Authority leads development of novel antibiotics for infections caused by biowarfare threat agents.

Currently, ceftazidime-avibactam, which the FDA approved in 2015, is the only antibiotic on the FDA Essential Medicines list effective against multi-drug resistant organisms. Executive Order (EO) 13944, "Combating Public Health Emergencies and Strengthening National Security by Ensuring Essential Medicines, Medical Countermeasures, and Critical Inputs Are Made in the United States" (2020), directed the FDA to develop the Essential Medicines list. The goal of this list is to ensure access to critical medicines and medical products that would be needed during a national emergency, prioritize allocation of resources, and encourage research and development (R&D) efforts (FDA, 2022). Under the EO, the SecDef was directed to restrict procurement of these products to domestic sources under the authority of section 225.872-1(c) of the Defense Federal Acquisition Regulation Supplement (DFARS), which will facilitate the Department's ability to prioritize procurement.

As another limiting factor, during the coronavirus disease 2019 (COVID-19) pandemic, the DoD was pushed to "regular customer" status for almost all supplies, including critical drugs. To reduce likelihood of similar issues arising in the future, DoD conducted assessments like the DoD-funded onshoring report that examined material availability factors (e.g., manufacturing capacity, sourcing of small molecule active pharmaceutical ingredients (APIs), and fill/finish capacity) during the COVID-19 crisis. DoD will consider other possible assessments as funding becomes available.

The Defense Logistics Agency (DLA) Troop Support medical supply chain worked with industry to develop a tool, Provenance Pharmaceutical Solutions (PPS), to provide visibility and analytics by mapping the country of origin and sources of supply of APIs and key materials and ingredients (Welski, 2023). PPS can completely map all drugs from the FDA Essential Medicines list.

Force health protection could be placed at risk if acquisition of novel antibiotics is prioritized over other programs. For instance, acquisition of novel antibiotics could displace procurement of other therapeutics on the Joint Deployment Formulary if prioritized over other biodefense preparedness products and efforts. In contrast, a risk to readiness exists if novel antibiotics are not prioritized. De-prioritization of novel antibiotics could lead to reduced R&D across the threat space which could result in the threat outpacing readiness.

Past military conflicts demonstrate that complications from battlefield wounds, including infections, contribute to prolonged convalescence, long-term disabilities, and combat

ineffectiveness. The current commercial landscape does not provide sufficient incentive to drive investment from industry. DoD investment in this area is critical to field novel antibiotics to counteract increasing threats. Prioritizing other programs over novel antibiotics may lead to casualties that exhibit degraded wound care, increased amputations, increased surgeries (Weintrob et al., 2018), and more lost duty days (Carr et al., 2003).

2. Feasibility of Domestically Sourced Ingredients

Request 2: The feasibility of prioritizing the procurement of novel antibiotics produced with domestically sourced ingredients and that are commercially available within the U.S.

It is feasible for the DoD to prioritize the procurement of novel antibiotics produced with domestically sourced ingredients; however, several challenges exist that make prioritizing procurement difficult. Pharmaceutical companies have cited several barriers to domestic production of novel antibiotics. These include U.S. environmental regulations related to API production, the large manufacturing platform footprint, domestic availability of materials, and costs. As of August 2019, 28 percent of the manufacturing facilities making all APIs to supply the U.S. market were in the United States (Safeguarding Pharmaceutical Supply Chains in a Global Economy, 2019). The remainder are in the European Union (26 percent), India (18 percent), China (13 percent), and other nations (15 percent). Notably, the number of registered facilities in China has doubled since 2010 and is expected to continue to grow under several Chinese initiatives.

Manufacturers with the capability to produce APIs or novel antibiotics operate in the United States; however, not all these sites are U.S.-owned. In prior years, manufacturers have received financial support to develop essential medicines and/or ramp-up and sustainment of production efforts. For example, private manufacturers such as Phlow Corporation and Paratek Pharmaceuticals received Federal funding via contract awards to support domestic production of novel antibiotic and essential medicines efforts. With this support, Phlow and their partners were able to deliver more than 1.6 million doses of medicines to the Strategic National Stockpile to treat COVID-19 (Phlow Corporation, 2020). Funding received by Paratek Pharmaceuticals supported onshoring the manufacturing supply chain and procurement of up to 10,000 treatment courses NUZYRA, a recent FDA-approved novel antibiotic (Paratek Pharmaceuticals, AInc., 2021).

Additional solutions to enable increased domestic production include establishing capacity within the industrial base to meet rapid scale-up and implementation of advanced manufacturing technologies. Examples of these technologies include flexible manufacturing facilities (e.g., small molecule, large molecule, and multiple products) and miniaturized/rapid manufacturing such as fed-batch culturing. Maintaining advanced manufacturing technologies would likely require financial support with long-term investments in manufacturing and production capabilities.

3. National Defense Stockpile

Request 3: The feasibility of procuring and maintaining novel antibiotics to be held within the National Defense Stockpile.

It is not currently feasible to procure and maintain novel antibiotics to be held within the National Defense Stockpile (NDS). The NDS was established "to decrease and to preclude… dangerous and costly dependence… upon foreign sources or a single point of failure for [critical materials] in times of national emergency" (Strategic and Critical Materials Stock Piling Act, 1939). It primarily stores rare materials such as chromium, germanium, and quartz, and tracks availability of rare materials used to manufacture products.

Potential issues exist with respect to inclusion of novel antibiotics in the NDS, relating to their compliance with FDA requirements (e.g., Current Good Manufacturing Practice) for transport, storage, and maintenance of pharmaceuticals. Storage and maintenance of APIs and antibiotics require specific controls that can vary between products. These controls include temperature and humidity levels, blocking exposure to other materials, periodic testing of potency, tracking of expiration dates, and mechanisms for disposal and replacement of expired products. These may require facilities and personnel not currently available at the NDS.

4. Statutory Authority Requirement

Request 4: Any statutory authority required for the Department to prioritize procurement of novel antibiotics produced from domestically sourced ingredients or to maintain a supply of such antibiotics.

Under EO 13944 (2020), the SecDef was directed to restrict procurement of critical medicines and medical products to domestic sources when necessary for national defense reasons, under section 225.872-1(c) of the DFARS. However, existing DoD policy does not address current pharmaceutical manufacturing and supply issues. The COVID-19 pandemic highlighted the lack of diversification in the medical product supply chain. For example, during the pandemic more than 97 percent of seamless plastic surgical and medical gloves, 90 percent of tetracyclines, and 62 percent of penicillin were imported from China (CATO Institute, 2020).

The DoD primarily receives pharmaceuticals through a prime vendor. During medical product shortages and increased demand of the COVID-19 pandemic, DoD was forced to work directly with suppliers because vendors were able to sell to other customers at a higher price.

Pharmaceutical companies have cited several factors that impact their ability to source or manufacture products in the U.S. that are outside of the purview of the DoD (U.S. Department of Commerce, 2011). Domestic manufacturing of antibiotics would require a whole of Government response to maximize success because the scale of available API appears limited more by the market and price of the final product than by other factors.

5. Other Recommendations or Data

Request 5: Any other recommendations or data surrounding the procurement of novel antibiotics as determined by the Secretary.

PPS, the pharmaceutical quality assurance platform developed by DLA Troop Support medical in collaboration with Supply Dynamics, provides visibility and analytics to determine the country of origin and sources of supply of API, key starting materials, and excipients (Gonzalez, 2022). The program provides early warning detection of risks and potential supply disruptions due to man-made or natural disaster events and provides an overall risk analysis score for each ingredient and key material. This tool will be useful to the DoD as they continue to investigate the feasibility of domestic production and procurement of novel antibiotics (Welski, 2023). The DoD is continuing to analyze current processes and policies with input from stakeholders to determine the best methods for prioritizing manufacturing and procurement of domestically sourced novel antibiotics and APIs.

Firms and databases used by the pharmaceutical industry, such as Citeline or Trialtrove, assess which companies are making medical products. These databases provide insights and prioritization based on drug candidates' maturity and applicability and assess FDA reports on manufacturing tracking and inspection that can identify where an API is produced. The pharmaceutical industry makes extensive use of these databases when drafting a business case to invest in a product, while the Government used them to prioritize COVID-19 candidates early in the pandemic.

D. CONCLUSION

The DoD fully recognizes the threat posed by antimicrobial resistance and identified the following key priorities for advancing development and procurement of domestically produced novel antibiotics.

1. **DoD investment into novel antibiotics is critical** due to the limits of commercial development. Failure to prioritize investment into novel antibiotics risks increased battlefield mortality rates from infections following surgical repair of complex soft tissue and bone injuries.

2. **DoD support of manufacturing capabilities need to improve** to enable a timely ramping up of domestic production. Although manufacturing facilities exist, manufacturers may require assistance through DoD loans or contact awards.

3. **Identify opportunities to engage with researchers investigating broad-spectrum, novel antibiotics** to further discovery of medications that could replace multiple antibiotics and minimize overall storage needs.

4. **Examine medical stockpiling capabilities** available to the DoD.

5. **Conduct a DoD policy review to identify pharmaceutical manufacturing and supply guidance** to evaluate policies relevant to: 1) supply chain diversification; 2) transparency from pharmaceutical suppliers and manufacturers; 3) vendor requirements to sell to the DoD during shortages; 4) timely communication on potential supply chain disruptions or shortages; and 5) application of FDA rules and processes to the DoD.

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