ANTIMICROBIALS
WORKING GROUP

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Re: Notice of Request for Public Comments on Section 232 National Security Investigation of Imports of Pharmaceuticals and Pharmaceutical Ingredients

The Antimicrobials Working Group (AWG) offers this submission in response to the request by the U.S. Department of Commerce for comments on section 232 national security investigation of imports of pharmaceuticals and pharmaceutical ingredients. AWG is a 501(c)(6) organization comprised of emerging antimicrobial therapeutics and diagnostics companies. Our membership is committed to improving the regulatory, investment, and commercial environment for antimicrobial drug and diagnostic device development.

AWG appreciates the Administration's goal to onshore production of essential medicines and pharmaceutical products to reduce the United States' dependence on foreign adversaries for critical components of the biopharmaceutical supply chain. During his remarks on April 2, President Trump specifically mentioned onshoring production of antimicrobials, a critical subset of medicines that has experienced significant drug shortages – approximately 42% more than in other drug classes – with 37 antibiotics currently in limited supply.[1]

Our coalition wishes to provide additional understanding of the intricacies of new and innovative antimicrobial drug development and the existing challenges in commercializing these drugs in the United States. Additionally, AWG proposes a limited, interim exclusion on tariffs for new antimicrobials to prevent further disruption to the commercial marketplace. As the Administration seeks to onshore biotechnology supply chains, AWG is committed to ensuring sustained and appropriate access to new antimicrobials for vulnerable patient populations.

1 Goldstein, David. "Why We Have Antibiotic Shortages and Price Hikes, and What One Very Enterprising Doctor Did in Response." HIV & ID Observations, 8 Oct. 2024, blogs.jwatch.org/hiv-id-observations/index.php/why-we-have-antibiotic-shortages-and-price-hikes-and-what-one-very-enterprising-doctor-did-in-response/2024/10/08/. Accessed 23 Apr. 2025.

I. A Pipeline of New, Active Antimicrobials Is Essential to Public Health

Antimicrobial agents – antibiotics and antifungals – remain a cornerstone of public health, providing critical tools to control infectious diseases and enabling modern medical procedures. Without effective antimicrobials, routine surgeries, cancer chemotherapy, and the care of immunocompromised patients would carry substantially higher risks from infection. Since their introduction, antimicrobials have significantly reduced morbidity and mortality from bacterial diseases. However, continuous innovation is required because pathogenic organisms constantly evolve, creating resistance to existing drugs -- a phenomenon known as antimicrobial resistance (AMR). As such, new antimicrobial products play a critical role in improving healthcare outcomes while also ensuring the nation is prepared to respond to public health emergencies (PHEs).

In the United States, over 2.8 million antimicrobial-resistant infections occur each year, and more than 35,000 people die annually as a direct consequence.[2] AMR infections are also a primary or associated cause of death in 50% of patients with cancer.[3] This burden is exacerbated by the slow pace of new antimicrobial development, described below, and the emergence of pathogens resistant to most available treatments. Experts warn that the current pipeline of antimicrobials is insufficient to meet the growing threat of resistance, largely due to scientific hurdles and economic disincentives[4].

There have been several recent instances of specific pathogenic outbreaks necessitating the use of new antimicrobial agents. *Candida auris* is a fungus that can cause serious bloodstream, skin, and other infections and is often multi-drug resistant (MDR). In 2023, there were 4,514 clinical cases of *Candida auris* in the United States, representing an 846% increase since 2019.[5] *Pseudomonas aeruginosa* is a strain of bacteria that can cause infections in the lung or blood or other parts of the body post-surgery and is often drug resistant. In 2023, contaminated eyedrops caused severe *Pseudomonas aeruginosa* infections in at least 68 patients in 16 states, including eight who suffered permanent vision loss, four who needed surgical removal of their eyeball, and three deaths.[6] These specific infections were highly drug resistant, demonstrating sensitivity to only one antibiotic. *Shigella* are bacteria that cause the infection shigellosis, which often manifests itself as a stomach bug. Extensively drug-resistant strains of Shigella have increased since 2015.[7]

Antimicrobial products also serve an indispensable role in health security and biodefense during PHEs. Secondary bacterial infections during chemical, biological, radiological, or nuclear (CBRN) incidents can cause significant morbidity and mortality. For example, many influenza-

[2] Centers for Disease Control and Prevention. *Antimicrobial Resistance Facts and Stats.*
[3] Nanayakkara, AK, Boucher, HW, Fowler, VG, Jezek, A, Outterson, K, Greenberg, DE. Antibiotic resistance in the patient with cancer: Escalating challenges and paths forward. CA Cancer J Clin. 2021: 71: 488- 504. https://doi.org/10.3322/caac.21697
[4] Dutescu IA, Hillier SA. Encouraging the Development of New Antibiotics: Are Financial Incentives the Right Way Forward? A Systematic Review and Case Study. Infect Drug Resist. 2021 Feb 5;14:415-434. doi: 10.2147/IDR.S287792. PMID: 33574682; PMCID: PMC7872909.
[5] Centers for Disease Control and Prevention. *Tracking C. auris.*
[6] National Eye Institute. *Eye experts weigh in on artificial tears in midst of infectious outbreak.*
[7] Centers for Disease Control and Prevention. Increase in Extensively Drug-Resistant Shigellosis in the United States

related deaths are attributable to secondary bacterial pneumonia, which has become increasingly challenging to treat due to rising AMR[8]. Since COVID-19, AMR has become more prominent in the U.S. healthcare system. In 2020, hospital-onset drug-resistant infections and deaths increased 15%. If an antimicrobial-resistant pathogen were weaponized, current treatment options could be quickly overwhelmed. In the event of other mass CBRN casualty events, severe injuries (wounds or burns) carry a high risk of infection, and these risks are compounded when bacteria are drug-resistant. Effective new antimicrobials are therefore a critical component of preparedness, ensuring that infections can be treated under emergency conditions and not allowed to exacerbate a crisis.

To address the gap in antimicrobial innovation, the U.S. government has established targeted programs that support the development and stockpiling of new antimicrobials. Created in 2006, the Biomedical Advanced Research and Development Authority (BARDA), bridges the gap between early research and the public availability of medical countermeasures. Through public-private partnerships, BARDA has supported six new antibiotics and antifungals that have achieved FDA approval in the last decade.[9] Many of these candidates are broad-spectrum agents intended to treat routine drug-resistant infections as well as high-priority biological threat pathogens. Complementing BARDA's advanced development support, the Project BioShield program provides a mechanism for the government to fund late-clinical-stage development and guarantee a market for crucial medical countermeasures (MCMs) by procuring them for national preparedness. Under Project BioShield contracts, new antimicrobials have been developed and purchased for the Strategic National Stockpile (SNS) to ensure treatments are available for drug-resistant biothreat agents (e.g. pulmonary anthrax) and secondary infections in emergencies. More recently, BARDA has supported efforts to onshore new antimicrobials in light of the market fragility that constrains companies from undertaking these activities independently. Furthermore, BARDA specifically underscored the need "to generate domestic production of critically needed antibacterial products" as a part of its Five-Year Strategic Plan.[10]

II. Innovative and New Classes of Antimicrobials Face Unique Market Challenges Relative to Biopharmaceutical Development

Newly developed antimicrobials are inherently used sparingly in clinical practice. This is a deliberate strategy to slow the emergence of resistance: physicians reserve new antimicrobials as a last resort when patients fail to respond to generic treatments. Stewardship guidelines also emphasize that new antimicrobials should be used sparingly to preserve their effectiveness.[11] Consequently, unlike many biopharmaceuticals that may be widely prescribed, new antimicrobials typically see low sales volumes after FDA approval. This contrasts with generic

[8] Morris DE, Cleary DW, Clarke SC. Secondary Bacterial Infections Associated with Influenza Pandemics. Front Microbiol. 2017 Jun 23;8:1041. doi: 10.3389/fmicb.2017.01041. PMID: 28690590; PMCID: PMC5481322.
[9] Biomedical Advanced Research and Development Authority. April 27, 2023.
[10] BARDA Strategic Plan 2022– 2026. pp. 15. Accessed at: https://faolex.fao.org/docs/pdf/us218400.pdf
[11] Majumder MAA, Rahman S, Cohall D, Bharatha A, Singh K, Haque M, Gittens-St Hilaire M. Antimicrobial Stewardship: Fighting Antimicrobial Resistance and Protecting Global Public Health. Infect Drug Resist. 2020 Dec 29;13:4713-4738. doi: 10.2147/IDR.S290835. PMID: 33402841; PMCID: PMC7778387.

antimicrobials, which are prescribed in high volumes for common infections (e.g. penicillins, cephalosporins) and are produced at large scale. The intentional restraint in using new antimicrobials for stewardship reasons means that a breakthrough drug could spend years on the market with only limited uptake in hospitals. Unlike other drug categories where a new therapy can rapidly recoup its development cost through broad usage, a new antimicrobial's life-saving value is not reflected in its sales volume. This fundamental difference underpins many of the economic challenges discussed below.

Current investment in innovation to develop a pipeline of new active antimicrobials is limited. The risk is higher and the rewards of investment are lower for antimicrobials than other types of therapeutic drugs because of reimbursement and market access challenges encountered *after* FDA approval. New antimicrobials used in inpatient hospital payment settings are reimbursed via Medicare Part A bundled payments, which assigns a fixed payment for a specific episode of care. This setting represents the most critically ill patients developing infections, where survival may be lowest. The use of a newer antimicrobial product may often exceed the cost of this fixed payment, potentially creating an incentive to use less expensive options or restrict formulary access for newer products. Patients often have to first fail treatment with older, cheaper, and variably active antimicrobials to gain access to newer antimicrobial products. This delay may be too late for some patients.

These marketplace dynamics result in sponsors of new antimicrobials R&D unable to recoup their investment under traditional volume-based payment structures for drugs. Currently, small and medium-sized biotechnology enterprises (SMEs) account for 80% of new antimicrobial drug discoveries, with 8% being discovered by non-profit institutes and universities, and 12% originating from large companies.[12] Since 2010, every SME has either gone bankrupt or exited the marketplace below investment cost.[13] The loss of these products represents a two-fold risk: a growing public health risk if products are removed from the U.S. marketplace, and an economic and intellectual property risk associated with the outflow of talent and scientific expertise, resulting in industry-specific skilled workforce challenges. In the event of a biological threat, given the role of antimicrobials in a public health emergency (PHE) response, the United States would also face a potential biosecurity risk if the federal government did not have access to new AMR products.

III. AWG's Response to the Bureau of Industry and Security (BIS) Regarding the Impact of Current Trade Policies on Domestic Production of Pharmaceuticals and Pharmaceutical Ingredients, and Whether Additional Measures, Including Tariffs or Quotas, Are Necessary to Protect National Security

The supply chain of new antimicrobials remains heavily dependent on foreign production, despite their critical importance in reducing morbidity and mortality from bacterial diseases. The

[12] The State of Innovation in Antibacterial Therapeutics. BIO Industry Analysis. February 2022.
[13] Outterson K, Orubu ESF, Rex J, Årdal C, Zaman MH (2021) Patient access in fourteen high-income countries to new antibacterials approved by the FDA, EMA, PMDA, or Health Canada, 2010-2020. Clin Infect Dis, ciab612. https://doi.org/10.1093/cid/ciab612

active pharmaceutical ingredients (API) of antimicrobials – the core active drug substances formulated into finished dosage form (FDFs) – are manufactured overseas, regardless of whether the drug is a generic or a newly-approved product. Production of APIs is the most resource-intensive step of antimicrobial drug production, utilizing complex chemical processes or microbial fermentation. Nearly all antimicrobial APIs used in U.S. medicines are imported.[14] Raw materials and key starting materials (KSMs) – used to develop API – are also manufactured outside the U.S. and similarly require the use of specialized equipment.

Due to cost and capability considerations, many SMEs must partner with overseas contract manufacturers to obtain API and the starting (chemical) materials used in the manufacturing process. While AWG appreciates the goal of onshoring pharmaceutical production to optimize supply chain security, it is important to recognize that relocating antimicrobial manufacturing to the United States faces significant regulatory and technical hurdles. These barriers include:

- **Regulatory Hurdles**: Any new U.S. manufacturing plant must meet Good Manufacturing Practice (GMP) standards and obtain FDA qualification before its product can be used in FDA-approved drugs. This regulatory process presents a further obstacle for antimicrobials as the resources and time needed to qualify a new facility will further delay availability of product for patients.
- **Capital Investment Hurdles:** Current manufacturing capacity is specifically designed to meet anticipated demand for a product. Given that antimicrobial products are utilized at low volumes, requisite product demands are met with current capacity. Building a new facility would require a significant investment, one which would be unlikely to be recouped through current sales volumes.
- **Technical and Economic Feasibility:** The United States presently lacks some of the industrial infrastructure and experienced workforce for certain antimicrobial production methods. Without significant government incentives or guaranteed purchase agreements, antimicrobial SMEs cannot sustain a domestic manufacturing plant solely for the production of commercial drugs. In economic terms, onshoring production of a low volume, highly specialized, potentially life-saving, product is not cost-competitive when compared to utilizing existing infrastructure abroad.
- **Need for Dedicated Manufacturing Facilities:** Additionally, some antimicrobials require dedicated, single-purpose manufacturing facilities. This is required for penicillin, cephalosporin, and carbapenem antibiotics, which as a group constitute the most common classes of antibiotics used in U.S. hospitals. Furthermore, most antimicrobials approved by the FDA between 2010 – 2025 by SMEs have no in-house manufacturing capabilities. They are dependent on contract manufacturing that largely occurs outside the United States.

[14] Kumar V, Bansal V, Madhavan A, Kumar M, Sindhu R, Awasthi MK, Binod P, Saran S. Active pharmaceutical ingredient (API) chemicals: a critical review of current biotechnological approaches. Bioengineered. 2022 Feb;13(2):4309-4327. doi: 10.1080/21655979.2022.2031412. PMID: 35135435; PMCID: PMC8973766.

Among new antimicrobials, the lone partial exception to overseas production is omadacycline (Nuzyra). With support from BARDA, Nuzyra's manufacturer recently completed onshoring manufacturing to the United States[15]. This was achieved under a Project BioShield contract that invested in domestic production capacity as a national preparedness measure.

Aside from Nuzyra's BARDA-supported facility, the manufacturing of all other new antimicrobials and antifungals are dependent on foreign production. Unlike many manufacturing sectors, additional tariffs applied to AMR drugs could further restrict their availability, as well as investment for new drugs. Dormant U.S. plants could not instantly adapt their manufacturing schedules to take on production of these antimicrobials. In most cases, no U.S. production capability exists. Given the earlier noted barriers, it would take considerable time to establish domestic manufacturing lines for each of these drugs. In the interim, there would be increased risk of supply disruption.

Recommendation 1: Interim Tariff Exemption for New Antimicrobials

To align with the intent of Title VIII of the Food and Drug Administration Safety and Innovation Act (FDASIA), titled Generating Antibiotic Incentives Now (GAIN), which recognized the public health threat of AMR by establishing the qualified infectious disease product (QIDP) designation under Section 505E of the Federal Food, Drug, and Cosmetics Act (21 U.S. Code § 355f(g)), AWG recommends an interim tariff exemption for new FDA-approved antimicrobials introduced since 2012.[16] QIDP is FDA's designation for new antimicrobials of special interest. The exemption is therefore narrowly tailored to ensure a negligible impact on overall import volume while maintaining the outsized benefit of access to new antimicrobials for PHEs.

AWG supports an interim exemption to align with national security objectives as industry works collaboratively with the U.S. government to bolster the antimicrobial supply chain. Such a policy would recognize the public health necessity and strategic importance of these therapeutics.

Recommendation 2: Incentives to Support Domestic Manufacturing of Antimicrobials

The added manufacturing challenges unique to antimicrobial drugs can be partially offset through federal grants, subsidies, and loans that would incentivize domestic and allied infrastructure. AWG supports additional funding to the Administration for Strategic Preparedness and Response (ASPR) to carry out ongoing activities under BARDA as well as industrial base management and supply chain efforts to invest in medical product industrial base expansion capacities. Additionally, the International Development Finance Corporation's (DFC) low-interest loan model could also offer incentives to reduce the costs of capital expenditures associated with new facility construction. Additional legislative solutions specific to new

[15] Under BARDA Project BioShield Contract, Paratek Pharmaceuticals Completes Onshoring for Antibiotic NUZYRA https://medicalcountermeasures.gov/newsroom/2024/paratek
[16] U.S. Food and Drug Administration. *Generating Antibiotic Incentives Now, Required by Section 805 of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144), Department of Health and Human Services.*

antimicrobials, such as new long-term pull incentive models, would also reduce demand uncertainty and encourage investment in domestic manufacturing.

Appendix A: List of FDA Approved Antimicrobials (2012 – Present)

- **Bedaquiline (Sirturo)** – Approved 2012. A novel mechanistic antibiotic for multi-drug-resistant tuberculosis (first new TB drug class in over 40 years).
- **Dalbavancin (Dalvance)** – Approved 2014. A long-acting intravenous lipoglycopeptide antibiotic for serious skin infections, dosed once-weekly.
- **Oritavancin (Orbactiv)** – Approved 2014. Another long-acting IV antibiotic for skin infections (single-dose treatment), effective against resistant Gram-positive bacteria.
- **Ceftolozane/Tazobactam (Zerbaxa)** – Approved 2014. A combination of a novel cephalosporin plus a β-lactamase inhibitor, for drug-resistant Gram-negative infections (including Pseudomonas).
- **Ceftazidime/Avibactam (Avycaz)** – Approved 2015. A cephalosporin (ceftazidime) paired with a new β-lactamase inhibitor avibactam; active against certain carbapenem-resistant Enterobacteriaceae.
- **Meropenem/Vaborbactam (Vabomere)** – Approved 2017. A carbapenem antibiotic combined with a novel boronate β-lactamase inhibitor, for complicated urinary and abdominal infections caused by resistant Gram-negatives.
- **Delafloxacin (Baxdela)** – Approved 2017. A fluoroquinolone antibiotic with activity against MRSA and pseudomonas, for skin infections and later expanded for pneumonia.
- **Plazomicin (Zemdri)** – Approved 2018. A next-generation aminoglycoside antibiotic for complicated urinary tract infections, designed to overcome aminoglycoside resistance mechanisms.
- **Omadacycline (Nuzyra)** – Approved 2018. A modern tetracycline-class antibiotic (aminomethylcycline) for community-acquired pneumonia and skin infections; notable for oral and IV formulations.
- **Eravacycline (Xerava)** – Approved 2018. A fluorocycline antibiotic (tetracycline derivative) for complicated intra-abdominal infections, active against certain multi-drug resistant organisms.
- **Bedaquiline / Linezolid (Pretomanid)** – Approved 2019. A nitroimidazole antibiotic combined with an oxazolidinone antibiotic for treating highly drug-resistant tuberculosis (approved as part of a combination regimen for XDR-TB).
- **Lefamulin (Xenleta)** – Approved 2019. A first-in-class pleuromutilin antibiotic for community-acquired bacterial pneumonia, with IV and oral formulations.
- **Imipenem/Cilastatin/Relebactam (Recarbrio)** – Approved 2019. An older carbapenem antibiotic (imipenem) with a renal enzyme inhibitor (cilastatin) plus a new β-lactamase inhibitor (relebactam), targeting resistant Gram-negative infections.
- **Cefiderocol (Fetroja)** – Approved 2019. A novel siderophore cephalosporin antibiotic that chelates iron to penetrate bacterial outer membranes, used for complicated urinary tract and other resistant Gram-negative infections (often effective against *Acinetobacter* and *Pseudomonas* that are carbapenem-resistant).
- **Ibrexafungerp (Brexafemme)** – Approved 2021. A novel triterpenoid antifungal (first in its class) for vulvovaginal candidiasis, with ongoing studies for invasive fungal infections (*antifungal*).

- **Rezafungin (Rezzayo)** – Approved 2023. A next-generation echinocandin antifungal for invasive candidiasis, notable for once-weekly dosing and activity against *Candida auris* (*antifungal*)
- **Sulopenem etzadroxil - / Probenecid (Orlynvah)** – Approved 2024. An oral antibiotic for the treatment of uncomplicated urinary tract infection(s) (uUTI) caused by certain bacteria (Escherichia coli, Klebsiella pneumoniae, or Proteus mirabilis) in adult women who have limited or no alternative oral antibacterial treatment options.
- **Gepotidacin (Blujepa)** – Approved 2025. A triazaacenaphthylene bacterial type II topoisomerase inhibitor indicated for the treatment of uncomplicated urinary tract infections (uUTI).