

February 5, 2019

The Honorable Richard Neal
Chairman
Committee on Ways & Means
United States House of Representatives
2309 Rayburn House Office Building
Washington, DC 20515

The Honorable Kevin Brady
Ranking Member
Committee on Ways & Means
United States House of Representatives
1011 Longworth House Office Building
Washington, DC 20515

The Honorable Lloyd Doggett
Chairman
Subcommittee on Health
United States House of Representatives
2307 Rayburn House Office Building
Washington, DC 20515

The Honorable Devin Nunes
Ranking Member
Subcommittee on Health
United States House of Representatives
1013 Longworth House Office Building
Washington, DC 20515

Dear Representatives:

We are a diverse group of stakeholders representing public health, infectious disease doctors, and both large and small antibiotic developers. We are writing to urge you to move swiftly to enact a package of incentives that would sustainably reinvigorate the pipeline of antibiotics while ensuring patient access and appropriate stewardship. Reinvigorating the pipeline of antibiotics in development is more critical today than ever, as hard-to-treat bacteria continue to emerge. Antibiotics underpin modern medicine, and antibiotic resistance jeopardizes the entire health system. Without effective antibiotics, patients lose not just treatments for serious infections, but also all of those advances of modern medicine that rely on the ability to effectively treat and prevent infections, including organ transplantation, cancer chemotherapy, major surgery, and care of preterm infants and immunocompromised patients. New resistance threats continuously emerge, rendering many existing drugs ineffective and shrinking our treatment arsenal. Many patients have already run out of treatment options and lost their lives due to resistant infections.

In order to be prepared to address current and future threats, it is necessary to have a robust pipeline of new drugs. Already there are too few new antibiotics in development to treat the most dangerous infections. Of those drugs in development today, only 11 have the potential to address the most critical Gram-negative pathogens on the World Health Organization's priority list of antibiotic resistant pathogens, and based on historical trends, perhaps only 2 of those will ever make it to market. By comparison, the pipeline of cancer drugs exceeds 1,000.¹

Despite the urgent need for new antibiotics, the future of antibiotic development is grim. There has been a significant decline in private sector investment in antimicrobial research and development, including early venture capital investment, as well as investment by both biotechnology as well as established biopharmaceutical companies. Few major pharmaceutical companies remain engaged in antibiotic discovery and development, and small biotech firms, even those that have launched or are close to launching products, struggle to sustain a viable commercial enterprise.

Nearly all large pharmaceutical companies have left the antibiotics market, and the remaining small biotech firms are struggling to raise private funds. Those companies that remain face significant commercial challenges. This situation is driven by factors that are unique to antibiotics. Antibiotics to treat resistant infections are extremely difficult to develop, and the opportunities to recoup development costs and to make a return on investment are limited by the fact that, unlike many other types of drugs, antibiotics are generally used for a short duration. Additionally, new antibiotics are used sparingly to preserve their effectiveness and to slow the development of resistance. The potential market for

treatments for resistant infections is also constrained by the fact that these infections may initially be relatively rare, as well as difficult to diagnose, due to limited availability of appropriate diagnostics. Finally, the most frequent setting for the administration of antibiotics is the hospital, where reimbursement policy creates an incentive to not use the most clinically appropriate antibiotic. This reality has driven most companies to channel R&D resources toward therapeutic areas with higher potential return on investment. Recently key players in the antibiotic field have exited or eliminated their R&D programs, including AstraZeneca², Sanofi³ and Allergan.⁴

The challenges driving the departure of large pharmaceutical companies from this space are also experienced by small biotechnology companies. Most antibiotics in the pipeline⁵ – more than 80% – are from small companies, and roughly half of the pipeline companies are pre-revenue (meaning that they have no products currently on the market). Historically, small companies have brought antibiotics through initial stages of development and then partnered with large pharmaceutical companies, which provide the significant resources, infrastructure, and capital, to move the products through later-stage clinical development, secure FDA approval, and successfully commercialize the product. The exit of larger companies not only results in loss of research and development in those companies, but also eliminates a historical pathway for small biotechs to secure funding and get their discoveries to patients. As a result, small companies are struggling. For example, two small companies, Achaogen⁶ and Melinta,⁷ collectively responsible for five recently-marketed antibiotics, have both announced the closing of their antibiotic research and clinical development programs. Several other small companies with recently approved products are in jeopardy of shuttering their operations entirely in 2019. Many of these companies received significant funding to support their R&D programs from U.S. Government funders, including the Biomedical Advanced Research Development Authority (BARDA) and CARB-X. If they fail, it is likely to prompt the departure of what little private investment remains in the antimicrobial space, with disastrous consequences for the already inadequate pipeline.

The exodus of companies from the antibiotic R&D market not only presents an immediate loss of the development of urgently needed new antibiotics, but a longer-term loss of the expert scientific workforce and their research. This loss of human capital will make it difficult to restart effective discovery and development programs and to ensure that patients have the treatments they need.

Congress has recognized the need for action and has taken valuable steps, passing the Generating Antibiotics Incentives Now (GAIN) Act in 2012 to extend the market exclusivity period for certain antimicrobials and, four years later, creating the Limited Population Antibacterial Drug regulatory approval pathway to facilitate the development of antibiotics and antifungals for patients who have few or no treatment options. Congress has also increased funding for the National Institute of Allergy and Infectious Diseases (NIAID) and BARDA to support antibiotic R&D, including CARB-X. These have been meaningful steps but are not sufficient to ensure the robust R&D ecosystem that is needed to meet the need of today and tomorrow's patients.

Without additional action the market will not deliver the new antibiotics that patients will need. Numerous studies by economists and policy experts have called for “pull incentives” – meaning policy measures to increase the value of a marketed antibiotic.^{8,9,10} Not all of this value must come from the U.S., and a more modest short-term investment could help stabilize today's market. But given the significance of the threat antibiotic resistance poses to the American public, U.S. policymakers should act now to develop a package of incentives that jumpstart the development of critically needed antibiotics.

We, the undersigned, believe the solution requires a package of incentives that address both the short-term need to stabilize the market and policies to address the broken market that makes antibiotic development economically infeasible for both small and large companies. Unlike grants and other push incentives, post-approval pull incentives would reward only successful development of FDA-approved

antibiotics that meet high standards for novelty and public health importance. All efforts must be paired with careful stewardship to ensure the drugs are used appropriately. The ultimate goal is to create an ecosystem that supports sustainable discovery, development, and commercialization of novel, innovative antibiotics in order to preserve these vital drugs and the health care advances they make possible.

Key principles of a pull incentive package:

- 1) Incentives should be paid after FDA approval, rewarding only successful development of novel antibiotics that address the greatest public health need.
- 2) A package of incentives should aim both to stabilize today's novel antibiotic market and to ensure that viability of future development – meaning they must be substantial and viewed as highly valuable to private markets.
- 3) Economic incentives should provide predictability for drug developers – assurance that the company can commit R&D funds today, knowing that the economic incentive will be available if the new drug meets eligibility criteria.
- 4) Incentives must be aligned with appropriate antibiotic stewardship and surveillance.

We commit to working with Congress and the Administration to further develop and advance a package of antibiotic incentives, at least some of which must be enacted in 2019 to meet growing patient needs and help mitigate a public health crisis. Such a package could, for example, include a mix of tax incentives, novel pull incentives, reimbursement changes, and even a low-interest loan program, along with continued investment in NIAID and BARDA.

Addressing the economic challenges of antibiotic development will require multiple solutions and a long-term commitment. Inaction will only exacerbate the current situation, making future efforts more challenging and expensive. We, the undersigned, look forward to working with Congress to ensure that patients today and tomorrow have effective life-saving antibiotics.

Sincerely,

Achaogen
Antimicrobial Innovation Alliance
Antimicrobials Working Group – (Amplix Pharmaceuticals, Aridis Pharmaceuticals, Cidara Therapeutics Inc., ContraFect Corporation, Entasis Therapeutics Inc., Iterum Therapeutics Ltd., Melinta Therapeutics Inc., Motif Bio plc, Nabriva Therapeutics US Inc., Paratek Pharmaceuticals Inc., Qpex Biopharma Inc., SCYNEXIS Inc., Summit Therapeutics plc and VenatoRx Pharmaceuticals Inc.)
Biotechnology Innovation Organization
GlaxoSmithKline
Infectious Diseases Society of America
Merck
Pfizer Inc.
Shionogi Inc.
Spero Therapeutics
Tetraphase Pharmaceuticals
The Pew Charitable Trusts
Trust for America's Health

Cc: Members of the United States House of Representatives Committee on Ways & Means

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- ¹ PhRMA, “List of 2018 Medicines in Development for Cancer” (2018), <http://phrma-docs.phrma.org/download.cfm?objectid=BFD25420-602C-11E8-91120050569A4B6C>.
- ² John Carroll, “Whittled Down to Biotech Size, AstraZeneca’s Antibiotics Crew Starts Over as Entasis,” *FierceBiotech*, Jul. 01, 2015, <https://www.fiercebiotech.com/biotech/whittled-down-to-biotech-size-astrazeneca-s-antibiotics-crew-starts-over-as-entasis>.
- ³ Evotec AG, “Evotec and Sanofi Sign Definitive Agreement to Combat Infectious Diseases,” press release, June 18, 2018, <https://www.evotec.com/en/invest/news--announcements/p/evotec-and-sanofi-sign-definitive-agreement-to-combat-infectious-diseases-5695>
- ⁴ Michael Erman, “Allergan to Sell Women’s Health, Infectious Disease Units,” *Reuters Business News*, May 30, 2018, <https://www.reuters.com/article/us-allergan-divestiture/allergan-to-sell-womens-health-infectious-disease-units-idUSKCN1IV1TN>.
- ⁵ The Pew Charitable Trusts, “Antibiotics Currently in Global Clinical Development” (2018), <https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development>.
- ⁶ Achaogen, Inc., “Achaogen Announces Strategic Update to Align Operations with Commercial and Clinical Development Priorities,” press release, July 26, 2018, <http://investors.achaogen.com/news-releases/news-release-details/achaogen-announces-strategic-update-align-operations-commercial>.
- ⁷ Amber Tong, “Low Sales, High Cost: Melinta Slashes HQ Research Staff as it Struggles to Grow Antibiotics Revenue,” *Endpoints News*, Nov. 29, 2018, <https://endpts.com/low-sales-high-cost-melinta-slashes-hq-research-staff-as-it-struggles-to-grow-antibiotics-revenue/>.
- ⁸ Jim O’Neill, “TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS” (2016), https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf
- ⁹ DRIVE-AB, “Revitalizing the antibiotic pipeline. Stimulating innovation while driving sustainable use and global access” (2018), <http://drive-ab.eu/wp-content/uploads/2018/01/DRIVE-AB-Final-Report-Jan2018.pdf>.
- ¹⁰ Boston Consulting Group for German Federal Ministry of Health, “Breaking through the Wall. A Call for Concerted Action on Antibiotics Research and Development” (2017).