



January 7, 2019

Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
Office of the Assistant Secretary for Health
US Department of Health and Human Services
200 Independence Avenue SW
Room 715-G
Washington, DC 20201

Re: Request for Information on the National Action Plan for Combating Antibiotic-Resistant Bacteria

Filed electronically at www.hhs.gov.

Dear Members of the PACCARB:

On behalf of the Cystic Fibrosis Foundation, we write to provide comments in response to PACCARB's Request for Information on the next National Action Plan for Combating Antibiotic-Resistant Bacteria. We appreciate the opportunity to share our thoughts on this document update and commend the Advisory Council for taking steps to address the significant challenges associated with the rapidly growing problem of antibiotic-resistant bacteria.

Cystic fibrosis is a rare genetic disease that affects over 30,000 people in the United States. The buildup of thick, sticky mucus in the lungs characteristic of the disease makes people with cystic fibrosis more prone to bacterial infections. Many people with CF suffer from difficult-to-treat acute or chronic infections, which can become life-threatening if not addressed adequately.

The Cystic Fibrosis Foundation is a national organization actively engaged in the research and development of new therapies for cystic fibrosis, including new treatments to address pathogens that commonly infect patients with CF. The CF Foundation has been engaged in virtually every element of the research and development process, from preclinical discovery to identification of new therapeutics to conducting clinical trials as well as post-market surveillance and quality improvement studies.

While we have been fortunate as a community to have made great progress in the development of effective therapies for many people with CF, we are not yet done. The CF Foundation is dedicated to improving the quality of life and standard of care for individuals with CF. To this end, the Foundation has committed \$100 million over five years for our new Infection Research Initiative. This new initiative supports a number of research projects aimed at improving detection, diagnosis, prevention, and treatment of infections related to cystic fibrosis.

Goal 1: Slow the emergence of resistant bacteria and prevent the spread of resistant infections.

Priority 1: *Judicious use* programs at hospitals and care centers are developed with diverse patient needs in mind with respect to antibiotic use. Patients with CF tend to be high users of antibiotics due to the chronic infections characteristic of the disease. Both acute and chronic infections in people with CF can quickly turn into complex and life-threatening illnesses. Thus, preserving access to limited use antibiotics to treat resistant pathogens is critical for the CF community.

Done right, stewardship programs have the capability of ensuring that patients in need of antibiotics receive the appropriate treatment in a timely manner. In efforts to preserve the efficacy of limited use antibiotics, stewardship programs must also ensure that appropriate use of antibiotics not be hampered by stewardship efforts. It is crucial that stewardship programs promoting judicious use of antibiotics not take a ‘one size fits all’ approach. Different patient populations will have different antibiotic use needs. To this end, providers should strive to understand how the needs of patients with chronic infections differ from those with acute infections and how these needs may impact stewardship goals and measures.

Priority 2: Optimizing standards of care through improving understanding of what “*the right antibiotic at the right time at the right dose for the right duration*” looks like for different pathogens and for different patient populations. Research is needed to further understand appropriate antibiotic use, especially in complex infection cases. For individuals in the CF community suffering from chronic infections, long-duration and multi-drug antibiotic treatment courses are often required. In treating for nontuberculous mycobacteria (NTM) – a group of difficult-to-treat bacteria that commonly infect individuals with CF but rarely impact individuals in the general population – treatment typically requires a course of three antibiotics over the duration of a year or more. The need for long-term antibiotics to eradicate or control infection must also be balanced against side effects such as ototoxicity and renal function declines.

To aid this end, the CF Foundation is dedicating \$100 million over five years for our new Infection Research Initiative. Through this initiative, the Foundation supports a number of research projects aimed at improving standards of care, such as the STOP 2 study evaluating what antibiotic treatment durations are best for CF patients with pulmonary exacerbations. The Foundation also supports research into NTM and other difficult-to-treat infections commonly found in the CF community to aid clinician treatment decisions. The next National Action Plan should prioritize research efforts on care optimization to further understand what appropriate use looks like in various patient populations.

Goal 3 - Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.

Priority 1: Support the development of innovative technologies that allow for accurate and rapid detection of pathogens and diagnosis of respiratory infections in patients with comorbid conditions. For patients with CF, understanding when the detection of a given pathogen should prompt treatment requires access to sensitive diagnostic tools that can provide early and accurate diagnosis of infection. Individuals with CF can become chronically colonized with respiratory pathogens starting in childhood, and patients with CF may culture positive for a number of possibly harmful microbes. Infection diagnosis in CF can therefore become increasingly challenging when co-infections are present. The respiratory

complications characteristic of the disease result in an added layer of difficulty in diagnosing infections, as it can be challenging to determine when colonization is symptomatic and requires treatment. Determination of the disease-causing pathogen and best course of treatment can be complicated for these reasons. It is therefore critical to acknowledge the difference between detection and diagnosis.

An additional challenge with respiratory infection diagnosis in CF patients is related to diagnostic tool reliance on sputum samples. As individuals with CF gain access to effective modulators, it will become harder for those individuals to produce sputum during clinical visits necessary for testing for respiratory infections. Diagnostics that use alternative types of samples to test for respiratory infections, such as exhaled breath condensate, can help address a growing need for the CF community. The National Action Plan should prioritize the development of new methods for detecting the presence of harmful pathogens as well as tools for evaluating cause of illness.

Goal 4 - Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.

Priority 1: Support stronger incentives for antibiotic drug development. Products in the antibiotics pipeline would ideally be supported by a robust ecosystem of incentives to combat the low market, high societal value of novel antibiotic products as well as the scientific challenges affiliated with developing novel antibiotics. However, we should prioritize incentives that address the biggest challenges for products in the pipeline. Small biotech companies, which are more predominant in the antibiotic development arena, tend to need support most at early stages as well as a promise of financial incentive post-market introduction to help attract investors.

The next National Action Plan should prioritize early stage incentives to support and de-risk the initial stages of product development, especially during the transition from pre-clinical to clinical testing as current push incentives do not do enough to address the needs of sponsors here. The plan should additionally explore public and private payer reimbursement models for antibiotic products. In 2017, HHS recommended that payers adopt a reimbursement model that delinks payments from sales volume for antibiotics. The 2020-2025 National Action Plan should prioritize facilitation of reimbursement reform to improve market viability of antibiotic products. Suggestions made in the next action plan should be informed by these reimbursement reform recommendations.

Priority 2: Address areas of need throughout the drug development process, including basic science research, expanded early product development support, and clinical trial design requirements. While policy incentives are crucial for fixing the broken antibiotics market, it is also essential that we address other areas of need throughout the drug development process. The revised National Action Plan should continue to prioritize basic science investigation. Research that can shed light on how bacteria become resistant and on mechanisms for overcoming resistance is of particular interest, as the problems tied to the rise of antibiotic resistance will not disappear with the introduction of new antibiotic drugs alone. The development of nontraditional products that address factors of resistance will be key, but more basic research is needed on this front.

Early development phase interventions, while beneficial, have not been enough to stabilize the antibiotics drug development pipeline. Current successful practices and programs that assist sponsors

during early product development, such as CARB-X, could be expanded to cover additional sponsors or additional phases of development.

Finally, antibiotics face many challenges with traditional clinical trial designs and trial endpoints. Some sponsors have access to a simplified clinical trial process via the Limited Population Pathway for Antibacterial and Antifungal Drugs program, but not all antibiotic products qualify. For infections where antibiotics are already approved, new therapies need to complete non-inferiority or superiority studies. Powering these large and expensive studies with enough participants can be a challenge for infections that predominantly impact individuals with CF, such as NTM. The concomitant medications that are part of CF standards of care can also further complicate such studies. The revised National Action Plan should explore ways to address these challenges and others present in antibiotics clinical trials designs.

Once again, we commend PACCARB for its request for comments on the revised National Action Plan for Combating Antibiotic-Resistant Bacteria. The CF Foundation is dedicated to reducing the impact of resistant bacteria on the CF community, and we appreciate this opportunity to share our infection research goals and efforts.

Sincerely,

Mary Dwight

A handwritten signature in black ink, appearing to read 'Mary Dwight', with a stylized flourish at the end.

Senior Vice President of Policy and Advocacy
Cystic Fibrosis Foundation