DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
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STATEMENT OF

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BEFORE THE

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"EXAMINING WAYS TO COMBAT ANTIBIOTIC RESISTANCE AND FOSTER NEW DRUG DEVELOPMENT."

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INTRODUCTION

Mr. Chairman, Ranking Member DeGette, and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss the current state of antibiotic resistance and the need for new solutions to the current crisis.

To address the growing public health concern, on September 18, 2014, the Administration released the National Strategy for Combating Antibiotic-Resistant Bacteria (CARB), and President Barack Obama signed Executive Order 13675, which called for creation of a National Action Plan and established a Federal Task Force to draft and implement the action plan. FDA is actively engaging in these efforts in coordination with other Federal agencies.

The decline in antibacterial drug research and development (R&D) in the private sector, at a time when serious antibiotic resistant infections are on the rise, is a tremendous public health problem, resulting in a very serious unmet medical need. According to the Centers for Disease Control and Prevention (CDC), each year in the United States, at least two million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a result of these infections.

Antibacterial drugs are critically important across medicine, including in the care of premature infants and for use in surgery, chemotherapy, and organ transplantation. However, bacteria are adept at becoming resistant to antibacterial drugs, as highlighted by the recent identification of a patient in Pennsylvania infected with *E. coli* bacteria possessing the *mcr-1* gene. It is essential to

use antibiotics judiciously to slow the development of resistance. Moreover, new antibacterial drugs are needed to provide treatment options in cases where resistance has eroded the effectiveness of existing drugs.

The Challenges Impacting Antibacterial Drug Development

There are significant scientific and economic challenges impeding the development of new antibiotics. From a scientific standpoint, many patients with bacterial infections are very sick and need to begin antibiotic therapy immediately. However, enrolling a very sick patient in a clinical trial in order to evaluate new antibiotics at the same time they are very sick can be difficult because critically ill patients may be unable to provide informed consent.

From an economic standpoint, antibiotics are generally viewed as less profitable by companies and venture capitalists because of their relatively low price and because they are generally taken only for a short period of time and often only for one course of treatment by any given patient. Compare this to the long, dependable income stream from a diabetes medicine or a blood pressure medicine that patients often take for the rest of their lives, or the relatively high price associated with cancer and some antiviral drugs. These economic realities can make it challenging for a company to justify large expenditures for the development of drugs in this area, as a report from the Eastern Research Group (ERG), funded jointly by HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE) and FDA, affirms.[1]

[1] *http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm*.

Furthermore, the inappropriate use of antibacterial drugs can accelerate the development of antibiotic resistance. It is essential that we use antibiotic drugs prudently in order to preserve the effectiveness of these drugs. The ability of drug resistance to be transferred from one bacteria to another and spread among a population of patients is a phenomenon unique to infectious diseases. Judicious use of antibacterial drugs is essential, in both the human and animal sectors.

Use of Common Clinical Trial Protocols to Encourage Antibacterial Drug Development

A promising strategy for encouraging antibacterial drug development is the establishment of a clinical trial network that can operationalize common clinical trial protocols at a level of quality that matches the pharmaceutical industry and that can respond to future needs in an agile fashion. The quality of the network should be at a level where pharmaceutical companies welcome the opportunity to perform their core development program utilizing the common protocols that are housed within the clinical trial network. Such a clinical trial network would allow pharmaceutical companies to utilize shared expertise and infrastructure to study antibacterial drugs. The CARB calls out this specific approach to reducing obstacles faced by drug companies developing new antibacterial drugs and states that the U.S. Government will examine the feasibility of generating and applying master clinical protocols to multiple test groups of patients while sharing a common control group. Colleagues at the Office of the Assistant Secretary for Preparedness and Response's Biomedical Advanced Research and Development Authority (BARDA) recently published a request for information on an antibacterial drug clinical trial network to gather information to evaluate the costs and practical considerations involved in establishing such a network.

What FDA is Doing to Address the Current Challenges

Provisions in a law passed in 2012, commonly known as the Generating Antibiotics Incentives Now Act, or the GAIN Act, are helping to stimulate the development of new antibiotics. Under GAIN, certain antibacterial or antifungal drugs intended to treat serious or life-threatening infections can be designated as "Qualified Infectious Disease Products" (QIDPs). As part of its QIDP designation, a drug receives priority review[2] and is eligible for fast-track designation.[3] At the time of approval, a product with QIDP designation qualifies for an additional five years of marketing exclusivity, to be added to certain existing exclusivity periods under the Federal Food, Drug, and Cosmetic Act. To date, FDA has granted 107 QIDP designations for 63 different unique molecules.

Since GAIN was passed, FDA has approved five new antibacterial drugs and one new antifungal drug with the QIDP designation. Three of the five antibacterial drugs, Dalvance (dalbavancin), Orbactiv (oritavancin), and Sivextro (tedizolid phosphate), are intended to treat acute bacterial skin and skin-structure infections (ABSSSI) caused by methicillin-resistant *Staphylococcus aureus* and certain other types of bacteria. Zerbaxa (ceftolozane/tazobactam) is indicated for the treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal

[2] Priority-review designation directs overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions or for drugs that have a QIDP designation. Priority-review designation does not affect the length of the clinical trial period. FDA informs the applicant of a priority-review designation within 60 days of the receipt of the original BLA, NDA, or efficacy supplement.

[3] Fast-track designation is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. Once a drug receives fast-track designation, early and frequent communication between the FDA and a drug company is encouraged throughout the entire drug development and review process.

infection (cIAI). Avycaz (ceftazidime/avibactam) is indicated for cUTI and cIAI for patients who have limited or no alternative treatment options.

FDA is working hard to streamline requirements for clinical trials for studying new antibacterial drugs, and the provisions of the GAIN Act are being actively implemented, but much more is needed. There are still significant economic and scientific challenges in the development of new antibacterial drugs that need to be addressed. Additional approaches to reducing the costs of studying antibacterial drugs, such as common clinical trial protocols, could provide other important means to stimulate antibacterial drug development. We also need cutting-edge science to move forward the development of new and innovative antibacterial drugs, as well as alternative therapeutics to combat bacterial infections.

To help drive this effort, FDA is working with academia, regulated industry, professional societies, patient advocacy groups, and government agencies to advance the science of clinical trials for antibacterial drugs. For example, FDA has contributed to the efforts of the Biomarkers Consortium of the Foundation for the National Institutes of Health (FNIH) to develop new endpoints for studying antibacterial drugs. FDA also works closely with the Clinical Trials Transformation Initiative (CTTI), a key group of dedicated scientists focused on streamlining and advancing clinical trials for more efficient drug development. FDA and CTTI have partnered to initiate activities related to efficient design and conduct of clinical trials for testing new antibiotics. FDA has also teamed up with colleagues at the Brookings Institution's Engelberg Center for Health Care Reform and more recently the Duke-Margolis Center for Health Policy to galvanize the scientific community's efforts in new antibiotic drug

development. The first Brookings Council for Antibacterial Drug Development (BCADD) meeting was held in August 2012, and the Brookings Institution has continued to convene meetings focused on a range of antibacterial drug development issues.

As part of these collaborative efforts, FDA will conduct a two-day public workshop in July 2016 focused on facilitating antibacterial drug development for patients with unmet needs and developing antibacterial drugs that target a single species. Discussions will focus on potential development pathways, aspects of clinical trials including which patient populations to study, trial designs and endpoints, and the role of clinical trial networks in antibacterial drug development.

Encouraging the Development of New Antibacterial Drugs

Given the public health threat posed by antimicrobial resistance, it is necessary to consider new mechanisms for encouraging the development of new antibacterial drugs to address unmet medical needs in the treatment of serious and life-threatening bacterial infections. We look forward to ongoing engagement with consumers, clinical experts, researchers, industry, and others to achieve this goal.

As the Committee knows, one option that has been proposed is the establishment of a new Limited Population Antibacterial Drug (LPAD) program. It is our understanding that, as a general matter, drugs approved using an LPAD pathway would be based on more streamlined development programs that establish that the drug is safe and effective in a limited population of patients with serious or life-threatening infections and unmet medical needs.

Importantly, because LPAD drugs would be approved based on streamlined development programs, there would be more uncertainty about potential risks posed by the product. This may result in a positive benefit-risk profile in a limited population of patients with serious or life-threatening infections and unmet medical needs. However, the benefit-risk assessment would be different for a broader, more heterogeneous patient population with less serious manifestations of the infection and which has other treatment options. This distinction should be clearly conveyed to the provider community. A clear branding mechanism would convey accurately to physicians using the product the limitations of the data supporting approval, including the uncertainty and the unique benefit-risk profile associated with the drug. Such labeling is particularly important in the context of antibiotic drugs, where historical overuse has led to increased antimicrobial resistance.

Accelerating Development of Rapid Diagnostic Tests for Antibiotic Resistance

Rapid diagnostic tests are an essential component of combating antibiotic resistance. Specific goals for accelerating the development of these rapid diagnostics are identified in the CARB. Rapid diagnostics can aid in faster diagnosis of patients with antibiotic resistant infections and result in appropriate therapy being initiated earlier. Rapid diagnostics also serve an important role in identifying patients colonized with resistant isolates at entry to hospitals, such that patients can be isolated and transmission to other patients minimized. Perhaps even more importantly, rapid diagnostics may aid in differentiating viral infections from bacterial infections and substantially reduce the use of unnecessary outpatient antibiotic therapy.

Through release of guidance documents and several public workshops, FDA and industry have made great progress in this area, however, similar to drug development, there are significant challenges to the development and use of diagnostics relative to empiric antibiotic use. Strategies to incentivize development and use of new antibacterial drugs have similar parallels for diagnostics.

Expedited Updating of Susceptibility Test Interpretive Criteria (Breakpoints) To Maximize the Effective Use of Antimicrobial Products

Enabling physicians to select appropriate antibacterial drugs is critical to individual health, as well as the public health, as we continue to combat antimicrobial resistance. Generally, physicians rely on antimicrobial susceptibility test (AST) devices, which provide information about whether a bacterium is either susceptible or resistant to an antibacterial drug. The criteria used to determine susceptibility are commonly referred to as "breakpoints." This information helps physicians choose appropriate antibacterial drugs for treatment. The results of such testing is also important to identify patients with certain resistant bacteria that warrant additional infection control measures to prevent spread of their resistant bacteria to others.

Outdated breakpoints can cause numerous problems, such as interfering with the implementation of appropriate infection control procedures, which can increase the chances that problematic resistant bacteria can be spread to others. Hospitals need up-to-date breakpoint information in order to determine whether an infection is caused by a resistant pathogen, and to put appropriate infection control procedures in place for those antibiotic-resistant bacteria.

AST device manufacturers need to be able to incorporate up-to-date breakpoint information into their devices quickly. However, currently, it can take several years to do so. Under the current regulatory framework, each antibacterial drug manufacturer updates its drug labeling with new breakpoint information and only then does each device manufacturer update its device algorithms and labeling. Reviewing breakpoint labeling supplements for each individual drug product (even when it shares the same active ingredient(s), and thus, generally has the same breakpoints) is no small task. Moreover, the process begins with the submission of labeling supplements from the drug manufacturers.

This protracted process of manufacturers updating the product labeling for each antimicrobial drug product adversely affects the public health by delaying AST device manufacturers from being able to promptly update the breakpoint information in their devices. It utilizes both industry and Agency resources that could otherwise be used for antibacterial and antifungal drug development or reviews that could confer greater benefits for patients. We need a better, more modern and streamlined process to help AST device manufacturers incorporate up-to-date and comprehensive breakpoint information in their devices more quickly, in order to get this information to health care providers sooner for the care of patients.

Solution for Updating Breakpoint Information Faster

In order to address the problems with the current scheme for updating breakpoints, we need to take breakpoints out of the drug product label and utilize more rapid, electronic means of communicating this information. Posting breakpoint information on FDA's website could enable us to update breakpoint information more efficiently. As mentioned, many antibacterial drugs

have the same active ingredient(s), and thus the same breakpoints. Accordingly, as a general matter, breakpoints are neither proprietary, nor specific to a particular drug product. Therefore, if FDA posted appropriate breakpoints for penicillin or amoxicillin products on the Internet, then FDA could take one single action to update the breakpoints for multiple drug products with the same active ingredient simultaneously.

To help FDA ensure that it can update breakpoint information accurately and expeditiously, the Agency could leverage the work being done by standards-development organizations that develop breakpoints, and recognize them, when FDA agrees that they are appropriate. FDA would retain full authority to accept a standard in whole or in part, or to establish alternative breakpoints. In addition, companies could submit data to support alternative breakpoints, if they disagree with the recognized standard.

CONCLUSION

It is virtually undisputed that we are facing a public health crisis because of the rise of serious resistant infections and the simultaneous decline in R&D in this area. FDA is using the tools we have to begin to strengthen the antibiotic drug pipeline. However, more work is needed to improve the current climate, and FDA is looking forward to continuing to work with stakeholders to address this public health crisis.

I am happy to answer any questions you may have.