



**STATEMENT
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE
SUBCOMMITTEE ON HEALTH
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U.S. HOUSE OF REPRESENTATIVES**

**“21ST CENTURY CURES: EXAMINING WAYS TO COMBAT ANTIBIOTIC
RESISTANCE AND FOSTER NEW DRUG DEVELOPMENT”**

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INTRODUCTION

Mr. Chairman, Ranking Member Pallone, 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.

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. The impact of antimicrobial-resistant infections on affected patients and families is significant and tragic. According to the Centers for Disease Control and Prevention (CDC), each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections. Many more people die from other conditions that are complicated by an antibiotic resistant infection. As the Infectious Diseases Society of America (IDSA) reports, “The trends toward increasing numbers of infection and increasing drug resistance show no sign of abating. Resistant pathogens lead to higher health care costs because they often require more expensive drugs and extended hospital stays.”

Antibacterial drugs first became available during the 1930s and 1940s, offering a tremendous advance in medicine, and were soon adopted as the standard of care in the treatment of a variety of infectious diseases. Many infections that were previously fatal, or left individuals with severe disabilities, became treatable or preventable. Today, 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 so it is essential to use these drugs judiciously to delay 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.

Many factors contribute to the spread of antimicrobial resistance. Any use of an antibacterial drug can encourage the development of drug-resistant bacteria. So it is important that we use antibacterial drugs only when their benefits outweigh their risks. In some cases, doctors prescribe antibiotics either too frequently or for infections that do not warrant an antibiotic, such as infections caused by a virus such as influenza. Sometimes patients do not take their antibiotic regimen as prescribed, making it more likely that microbes will develop resistance. The use of subpotent or counterfeit antibiotics also can contribute to resistance; counterfeit antibiotics are a problem encountered particularly in the developing world. The injudicious use of important antibiotics in animal agriculture is also of particular concern. Through international trade and travel, resistant microbes can spread quickly worldwide. As of today, antimicrobial-resistance mechanisms have been reported for all known antibacterial drugs that are currently available for clinical use in human and veterinary medicine. FDA has partnered with CDC's antibiotic

stewardship programs, including the Get Smart Campaign—which seeks to ensure that all patients get the right antibiotic at the right dose for the right amount of time—to improve consumer and provider education around appropriate use. Antibiotic stewardship programs and education will always serve a critical role in preserving the effectiveness of antibiotic treatment, be it for penicillin or our newest antibiotic therapies.

In some cases, bacterial strains that are resistant to multiple antibacterial drugs have been isolated. Such multi-drug-resistant (MDR) pathogens represent a substantial public health threat. The lack of available antibacterial drugs to treat infections caused by MDR organisms—particularly MDR Gram-negative bacteria¹—that have spread widely through the U.S. health system, have created an area of urgent unmet medical need. Unfortunately, there are very few antibacterial drugs in the R&D pipeline with the capacity to treat these infections.

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 often very sick and need to begin antibiotic therapy immediately. But enrolling a very sick patient in a clinical trial at the same time can be very difficult.

¹ Gram-negative bacteria are a type of bacteria defined by their staining characteristics on microscopic examination.

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 take indefinitely, often 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 recent Eastern Research Group (ERG) report, funded jointly by HHS and FDA, affirms.²

Common medical practices that accelerate the development of antibiotic resistance, such as the inappropriate use of antibacterial drugs, are at odds with the public health goals of preserving the long-term effectiveness of these drugs. The ability of drug resistance to be transferred from one microorganism to another and spread among a population of patients is a phenomenon unique to infectious diseases. Judicious use of antibacterial drugs is essential.

However, the judicious use of antibacterial drugs is at odds with the traditional business models and marketing practices used by the pharmaceutical industry for other drug categories, and serves as just one more disincentive to investment in antibiotics. To address this phenomenon as well as to incentivize antibacterial R&D in general, various thought-leaders in the United States

² http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm.

and Europe have discussed new business models for antibacterial development that delink the sales of these drugs from companies' returns on investments (e.g., an insurance-type model, defense contractor model, antibiotic corporate bond/patent extension certificate financial model, and price for service model, rather than existing price for product model).³ Should such models be adopted in the future, they likely would include new ways of risk-sharing in antibiotic R&D, such as establishing public-private partnerships or new reimbursement models to pay for these essential medicines post-approval.

What FDA is Doing to Address the Current Challenges

Provisions in a law passed a little over two years ago, 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 review⁴ and is eligible for fast-track designation.⁵ At the time of approval, a product with QIDP designation may be

³ These delinking-type models were discussed at the September 1, 2014, Big Innovation Centre/Chatham House Workshop: “New Commercial Business Models for Antibiotics—What Can Be Learnt From Other Industries?” held in London, United Kingdom.

⁴ 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.

⁵ 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.

eligible for an additional five years of marketing exclusivity, in addition to certain existing exclusivity periods under the Federal Food, Drug, and Cosmetic Act. To date, FDA has granted 59 QIDP designations for 39 different unique molecules. In the past few months, FDA has approved three new antibacterial drugs with this beneficial QIDP designation. The three 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. It is wonderful to have so many QIDP designations and to have drugs approved that are benefitting from the designation. However, we also have to keep in mind that not all products in development ultimately make it to approval; more will be needed to meet patient needs.

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 more is needed. There are still significant economic and scientific challenges in the development of new antibacterial drugs that need to be addressed. Additional financial incentives, as well as new 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, CDER has assembled an Antibacterial Drug Development Task Force (Task Force), a group of expert scientists and clinicians from within FDA, to consider opportunities to help facilitate antibacterial drug development. FDA also has an Agency-wide Task Force on

Antimicrobial Resistance, which assures coordination of FDA activities across multiple product areas.

The Task Force is working with many leaders, including those drawn from academia, regulated industry, professional societies, patient advocacy groups, and government agencies. For example, FDA has contributed to the efforts of the Biomarkers Consortium of the Foundation for the National Institutes of Health (NIH) 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. As a result, FDA and CTTI have partnered to help convene a variety of important scientific meetings and initiate activities on vital topics related to efficient design and conduct of clinical trials for testing new antibiotics. Our Task Force has also helped FDA team up with colleagues at the Brookings Institution's Engelberg Center for Health Care Reform 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.

FDA and our Task Force members also have been busy on our own. In February 2013, we held a public meeting focused on creating an alternative approval pathway for certain drugs, such as antibacterial drugs, that are intended to address unmet medical needs. We also have asked

stakeholders for input; in May 2013, we issued a *Federal Register* Notice,⁶ seeking input from the public on a wide range of topics related to antibacterial drug development. Since the GAIN Act, FDA has generated 11 guidance documents for industry⁷ in draft and final form, which describe FDA's scientific thinking with regard to developing new antibacterial drugs.

As part of our Task Force's collaborative efforts, FDA is working closely with NIH to further advance the development of new antibacterial drugs. In July 2014, we jointly hosted a two-day Public Workshop to identify strategies for promoting clinical trials for antibacterial drugs and encouraging partnerships to accelerate their development. The Eastern Research Group (ERG) report was presented at the workshop and other specific issues were discussed, including:

- Priorities and strategic approaches to conducting clinical trials for antibacterial drugs
- Regulatory pathways, including streamlined development programs for antibacterial drugs for patients with limited or no treatment options
- Clinical trial design issues, such as the development of common clinical protocols; using common control groups; statistical analysis issues; sharing data across trials (and data standards); appropriate clinical trial endpoints; and lessons learned from other therapeutic areas

⁶ <https://www.federalregister.gov/articles/2013/05/31/2013-12925/new-approaches-to-antibacterial-drug-development-request-for-comments>.

⁷ <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm406769.htm>.

- The role of public-private partnerships in advancing the scientific and clinical trials enterprises.

The implementation of the GAIN Act and the work of the FDA Task Force have provided good first steps toward strengthening the antibacterial drug pipeline, and recent reports suggest that the pipeline is beginning to open up. But, we must do more. Additional attention to financial incentives, new approaches for studying antibacterial drugs (such as the creation of common clinical trial protocols), and streamlined development pathways will likely be needed to improve the climate.

Encouraging the Development of New Antibacterial Drugs

FDA recognizes its role in fostering the translation of scientific advances into the development of drugs that can treat disease and in considering novel approaches that might facilitate development of drugs that can treat unmet needs. Traditional drug development programs are designed to evaluate the benefits and risks of treatment with a high degree of precision for the full range of manifestations of a disease or condition. Often this will involve studies that expose a large number of patients to the drug. In some cases, such as when safety issues have arisen with prior drugs in a class or are noted in early clinical trials, additional trials are needed to help characterize potential serious, but infrequent, risks. Typically, these studies are needed when there is an expectation that the drug will be used broadly in patients with less severe manifestations of the condition.

Existing processes to expedite drug development and review of important new therapies have worked effectively in many circumstances, such as under the accelerated approval pathway, which permits drugs that are intended to treat serious or life-threatening diseases or conditions to be approved based on surrogate or intermediate endpoints. In addition, FDA's long-standing commitment to regulatory flexibility regarding the evidence required to support approval has effectively facilitated development of drugs for patient populations with serious unmet medical needs.

However, we can do more. Given the public health threat posed by antimicrobial resistance, FDA believes 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 under this proposal, as we understand it, 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. 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.

Expedited Updating of Susceptibility Test Interpretive Criteria (Breakpoints) To Maximize the Effective Use of Existing 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. As a general matter, a key part of the information that physicians use to select an antibacterial drug is whether the patient’s infecting bacteria is categorized as susceptible.

Outdated breakpoints can result in selecting a drug that may not effectively treat a patient's infection, and in serious or life-threatening situations, the patient could succumb to the infection or its complications. Outdated breakpoints can also interfere with the implementation of appropriate infection control procedures. 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. There are approximately 200 reference-listed antibacterial drug products and more than 400 generic copies of those products. 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 preventing AST device manufacturers from being able to promptly update the breakpoint information in their devices, and 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.

Recognizing the significant challenges involved in updating breakpoints, in 2007, as part of the Food and Drug Administrative Amendments Act of 2007 (FDAAA), Congress directed FDA to prioritize breakpoint labeling updates, and FDA has done so. Approximately 150 of 207 product labels for reference-listed drugs have been updated over the past seven years. However, bacteria evolve and develop new resistance mechanisms, so breakpoints can shift periodically over time. Accordingly, the process of updating breakpoint information in drug labeling is never-ending. So, even as we finish updating the initial 207 product labels, we will be re-updating product labels for some drugs that were updated in the last seven years.

Moreover, while health care providers will always encounter infections caused by a wider range of bacteria than those identified in clinical trials, currently, AST devices are generally only labeled for reporting information on the susceptibility of bacteria identified in clinical trials conducted for the approved indication(s). We need a better, more modern and streamlined administrative 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, FDA needs 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 Internet 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 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 to 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 tremendous public health crisis because of the rise of serious antibacterial 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.