ENGELBERG CENTER for
Health Care Reform
at BROOKINGS

Reinvigorating the Oral Antibacterial Drug Development Pipeline

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Discussion Guide

Introduction

Antibacterial drugs are a critical component of the nation's public health armamentarium and have saved millions of lives by preventing and treating a range of bacterial infections. However, antibacterial drug development has been hampered by challenges unique to the antibacterial drug market. First, the use of antibacterial drugs is likely to lead to drug resistance. In the context of widespread antibacterial drug resistance, it is necessary to use "second" or "third" line treatment options, some of which have less favorable adverse event profiles and are available only for intravenous administration. Second, efforts to preserve the effectiveness of antibacterial drugs by preventing inappropriate use – through stewardship programs, for example – are necessary to protect public health but may limit return on investment for drug development. A paradox exists whereby stakeholders simultaneously require the development of new drugs but also strict measures to limit their use. This paradox, coupled with other scientific, regulatory, and economic challenges, has stifled innovation and left patients and providers with fewer options to treat increasingly resistant infections. Overcoming the antibacterial drug paradox is critical for combatting antibacterial drug resistance, which results in 23,000 deaths[1] and over $50 billion in excess health spending and lost productivity annually.[2,3]

One consequence of the dwindling antibacterial drug development pipeline has been a reduction in effective oral antibacterial drug treatment options. The availability of oral drugs is critical in a number of situations, including the ambulatory care setting, and facilitating hospital discharge by transitioning patients from intravenous drugs. Recent proposals to reinvigorate the antibacterial drug pipeline are geared toward serious, life-threatening bacterial infections treated in the inpatient setting, which could lead to a greater focus on intravenous therapies. In order to thoroughly address existing unmet need and prevent future unmet need in the infectious diseases space, stakeholders must identify drug development approaches that promote a balanced mix of new oral and parenteral antibacterial drugs. Under a cooperative agreement with the U.S. Food and Drug Administration (FDA), the Engelberg Center for Health Care Reform at the Brookings Institution is convening this expert workshop to address scientific, regulatory, and economic challenges impeding oral antibacterial drug development and to identify potential approaches (e.g., regulatory strategies, economic incentives) to reinvigorate the oral antibacterial drug development pipeline.

The Need for Oral Antibacterial Drug Developement

Both oral and parenteral antibacterial drugs play an important role in patient care, and the selection of an oral versus a parenteral agent depends on the clinical situation. Oral administration is often easier and more convenient than the parenteral route, which generally requires drug administration by a trained health care professional. Catheters used to deliver intravenous antibacterial drugs carry their own risks—for example, they can become obstructed or infected. In the inpatient setting, early

transition of patients from intravenous to oral antibacterial drugs can reduce hospitalization time, which lowers health care spending and the risk of hospital-acquired infections and thrombotic complications.[4]

The rise of antibacterial drug resistance is a pressing concern for several infections where oral options are becoming increasingly limited. Gonorrhea, a common sexually transmitted disease that can cause severe reproductive complications, has been classified as an urgent public health threat by the Centers for Disease Control and Prevention (CDC).[5] Every year there are an estimated 820,000 gonococcal infections in the United States, which are associated with $162 million in lifetime direct medical costs.[6,7] Emerging resistance patterns have amplified concerns about gonorrhea despite a decreasing number of new cases due to educational efforts and prevention programs on sexually transmitted diseases.[8]

Gonorrhea has acquired resistance to a number of oral drugs that were once effective treatment options including tetracyclines and fluoroquinolones (e.g., ciprofloxacin). Given these emerging resistance patterns, in 2007 CDC updated its treatment recommendations for gonorrhea removing fluoroquinolones as an option and establishing ceftriaxone administered intramuscularly as the first line recommended treatment.[9] The emergence of cephalosporin-resistant gonorrhea represents a threat to public health.[8] New oral antibacterial drugs could address this threat by reducing the impact of resistance while providing patients and health care professionals with an alternative to parenteral therapy.

Infectious diseases caused by gram negative bacteria may be susceptible only to an antibacterial drug administered intravenously. CDC's characterization of carbapenem-resistant Enterobacteriaceae as an urgent antimicrobial resistance threat underscores the importance of new drug development in this area. Often patients have no options other than an antibacterial drug administered intravenously for their infectious disease. For example, patients with uncomplicated urinary tract infection caused by bacteria that are fully susceptible to antibacterial drugs often require a short course of oral antibacterial drug therapy. If the bacteria are resistant to antibacterial drugs administered orally, patients with uncomplicated urinary tract infections may require treatment with an antibacterial drug administered intravenously. This is another area in which oral antibacterial drug development can help address patient needs.

Certain infections require longer courses of antibacterial drug therapy, and the antibacterial therapy is often administered intravenously in order to achieve higher levels of the drug in certain tissues. An example of such an infection is acute osteomyelitis where intravenous administration of an antibacterial drug ensures adequate tissue penetration to the site of infection in the bone. New oral antibacterial drugs can be important in the armamentarium for these infections.

The availability of both intravenous and oral formulations of investigational antibacterial drugs might provide important advantages in the clinical development of new antibacterial drugs for treatment of serious infectious diseases. The availability of both intravenous and oral formulations of the investigational drug, whereby patients enrolled in a clinical trial can begin and complete the therapy with the investigational drug, may facilitate more robust conclusions about efficacy and safety of the investigational drug and provide treatment alternatives for patients.

Efforts to Stimulate Antibacterial Drug Development

New strategies aimed at mitigating antibacterial drug resistance are being explored both in the private and public sectors, and legislative proposals that seek to stimulate antibacterial drug development are currently under consideration in Congress. Two notable bills that have been introduced in Congress are the Antibiotic Development to Advance Patient Treatment (ADAPT) Act of 2013 and the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act of 2014. Already, a

number of antibacterial drugs have qualified for incentives under the Generating Antibiotic Incentives Now (GAIN) provisions of FDASIA, which was enacted in 2012.

Recognizing the persistent threat of antibacterial drug resistance, Congress enacted the GAIN provisions to provide companies with five additional years of market exclusivity for "qualified infectious disease products" (QIDP) that treat serious bacterial or fungal diseases. Further, GAIN attempts to expedite approval of these drugs by providing access to FDA's fast track and priority review programs.[10] Over the past several months, FDA has approved three new antibacterial drugs that qualified for incentives provided through GAIN.[11]

The proposed ADAPT Act provides for the approval of antibacterial and antifungal drugs for use in limited populations with life-threatening health conditions and unmet medical need. If enacted, drug sponsors could request approval through the Limited Population Antibacterial Drug (LPAD) mechanism, which was proposed by the Infectious Diseases Society of America in 2012. Essentially, the LPAD approval mechanism would allow for smaller, less costly, and faster clinical trials with data to support safety and efficacy in a limited population. Therefore, approval through this approach would necessitate mechanisms to ensure that prescribers were aware that use of the new antibacterial drug should be restricted to the population for whom it was approved. [12] The ADAPT Act includes labeling requirements to support this goal.[13]

The proposed DISARM Act differs from the ADAPT Act in that it focuses on reimbursement rather than regulatory incentives to spur antibacterial drug development. The bill utilizes a mechanism akin to the Centers for Medicare and Medicaid's (CMS) New Technology Add-on Payment (NTAP). The NTAP pathway was established because Diagnosis-Related Group (DRG) payments made to hospitals, which are based on historical data, do not always capture the value of new medical technologies. To address this challenge, the NTAP pathway allows CMS to pay for 50 percent of the cost of a new technology on top of the base DRG payment for up to 3 years.[14] Thus far, the antibacterial drug fidaxomicin is the only oral medication that has benefited from the NTAP pathway.[15] The DISARM Act follows the NTAP model but makes the add-on payment permanent for new antimicrobial drugs that meet the GAIN Act definition of a QIDP and treat infections that are associated with significant morbidity or mortality.[16]

Proposals to stimulate antibacterial drug development have been welcomed by many stakeholders; however, there are concerns about how they might affect the balance between new oral drugs and new intravenous antibacterial drugs. For example, language in the ADAPT Act suggests that new products approved through the LPAD mechanism might be therapies to treat seriously ill patients in hospitals and thereby are likely to be administered intravenously. While such drugs are needed, there may still remain an unmet medical need for oral antibacterial drugs. Further, the DISARM Act allows for add-on payments for innovative antibacterial drugs, but these payments are for drugs bundled into DRGs and paid to hospitals. Incentives would still be needed for antibacterial drugs primarily used in the outpatient setting.

Additional incentives and strategies may be required to support the development of a balanced mix of antibacterial drugs. One promising public-private partnership between the Biomedical Advanced Research and Development Authority (BARDA) and industry seeks to develop a portfolio of new antibacterial drugs rather than focusing on a single medical countermeasure.[17] There are also a number of economic incentives proposed in the 2014 President's Council of Advisors on Science and Technology (PCAST) report on combatting antibiotic resistance, several of which aim to delink antibacterial drug usage from a company's revenue. Such approaches have the potential to reinvigorate the drug development pipeline while promoting the appropriate use of these important resources.[18]

Workshop Objectives

This expert workshop is divided into three sessions. The first session will address the broad range of challenges hindering oral antibacterial drug development. The second session will explore scientific, regulatory, and other non-economic approaches to support oral antibacterial drug development. The third session will examine economic solutions to achieve this goal.

Session I

This session will explore the challenges to reinvigorating the oral antibacterial drug development pipeline. Existing proposals to spur drug development appear more geared toward parenteral therapies likely to be used in the inpatient setting. As a result, drug sponsors seeking to develop oral antibacterial drugs may require new incentives to support their efforts. This session breaks development challenges into three primary categories: scientific, regulatory, and economic. As part of the discussion, meeting participants will address the questions listed below:

Scientific Challenges:

- What are the scientific challenges encountered when developing an oral antibacterial drug?
- Are there manufacturing/formulation issues that make it more difficult to develop oral antibacterial drugs?
- How is the spectrum of activity considered when planning for developing an oral antibacterial drug?

Regulatory Challenges:

- To what extent would the availability of both intravenous and oral formulations of an investigational drug provide advantages in new antibacterial drug development for patients with unmet medical need?
- What is the potential role for streamlined development pathways for a new oral antibacterial drug without an intravenous formulation?

Economic Challenges:

- What are existing or potential incentives and/or disincentives for facilitating appropriate use (stewardship) of oral antibacterial drugs?
- How might currently available incentives (e.g., GAIN) affect the balance between oral and intravenous antibacterial drug development?

Session II

This session will focus on utilizing scientific methods, regulatory strategies, and other non-economic means to stimulate oral antibacterial drug development. The aforementioned PCAST report emphasizes that while the cost of clinical trials can be financially burdensome, one approach to reducing costs is to develop and leverage an advanced infrastructure for studying antibacterial drugs. One suggested strategy entails developing a national clinical trials network to achieve higher efficiency and lower overall costs when studying antibacterial drugs.[19] Such a system could enable researchers to disseminate clinical data, increase the effectiveness in identifying patients using innovative diagnostic tests, and would accelerate the process of including or excluding specific trial sites dependent on the extent of resistance in various locations. In session II, participants will address the following questions:

- How could master trial protocols/trial networks help drive the development of oral antibacterial drugs? Are there any unique challenges in this setting?

- What role do diagnostics play in supporting the development of oral antibacterial drugs and supporting stewardship?
- What role do PROs play in supporting the development of oral antibacterial drugs?

Session III

The antibacterial drug market is unique because of the development of resistance—for example, treating one patient with an antibacterial drug may make it less likely to be effective for other patients over time. Further, antibacterial drugs are generally inexpensive and have limited reimbursement incentives. To slow the spread of resistance, many health systems limit the use of certain antibacterial drugs for smaller groups of patients with particular infections. All of these factors have contributed to a weak antibacterial drug pipeline. This session will explore potential incentives as they pertain to oral antibacterial drugs. The session will also include discussion on antibiotic delinkage models,[20] which seek to delink antibacterial drug usage from a company's revenue. Meeting participants will discuss the following questions:

- What are the most promising reimbursement incentives for accelerating the development of oral antibacterial drugs while also encouraging limited use of these drugs?
- What is the value of upfront economic incentives versus pull mechanisms?
- How can we ensure that economic incentives work for both oral and parenteral antibacterial drug development?

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