

Brookings Council on Antibacterial Drug Development Meeting #1

Introduction and Background

Health care professionals and medical product developers have made significant strides in the treatment of infectious diseases, but additional antibacterial drug development still remains a critical area of public health. Several factors are eroding past gains and impeding further progress in the field, particularly the rapid emergence of new drug-resistant pathogens. Resistance can stem from the natural selective pressure on pathogens to evade or adapt to a course of treatment and the inappropriate use of antibacterial products. A 2004 report by the Infectious Diseases Society of America (IDSA) noted that of the two million hospital-acquired bacterial infections and 90,000 resultant deaths each year, an estimated 70 percent of these cases were resistant to at least one antibacterial product.¹ Problems with antibacterial resistance are especially challenging in cases where pathogens are resistant to multiple, if not all, available treatments.

Another factor hindering progress is the significant decrease in drug manufacturers' research and development programs for antibacterial drug discovery. This is due, in part, to the increasingly expensive and time-intensive nature of clinical trials, which require significant investment by product developers. The clinical trials process for antibacterial products is complicated by the need to quickly identify possible participants. The lack of rapid and reliable diagnostic tests that accurately identify specific infections effects both the selection of treatment options in the clinical setting and whether a patient is an appropriate candidate for a clinical trial. Without more definitive diagnostics, trials may enroll many patients who do not suffer from the trial's targeted infection or fail to enroll those patients who do. The relatively low pricing and short duration of a treatment regimen create a low return on investment for the products. Difficult economic conditions may push product developers to focus on more profitable areas of drug discovery. These economic and clinical trial characteristics have translated into a decrease in the number of antibacterial product approvals over the last several decades. An IDSA analysis conducted in 2004 demonstrates a decline from 16 New Molecular Entity systemic antibiotics approved in the five-year period from 1983 to 1987 to only two such product approvals between 2008 and 2012.²

As approved treatments become less effective and fewer new products are available, physicians have increasingly serious challenges in treating multi-drug resistance infections. Limited treatment options affect the general population but are of particular concern for specific clinical populations including

¹ Infectious Diseases Society of America. (2004). "Bad Bugs, No Drugs." Retrieved August 21, 2012, from http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=1&cad=rja&ved=0CFcQFjAA&url=http%3A%2F%2Fwww.idsociety.org%2FuploadedFiles%2FIDSA%2FPolicy_and_Advocacy%2FCurrent_Topics_and_Issues%2FAntimicrobial_Resistance%2F10x20%2FImages%2FBad%2520Bugs%2520no%2520Drugs.pdf&ei=6f4zUKymlKfb6wGf0IDYCW&usq=AFQjCNGp73pbtTAI5Ql-pLSlxcUQ4g-aEg&sig2=crVjxXmt0ABCNm0Ii6GIPg.

² Infectious Diseases Society of America. (2011). "Combating Antimicrobial Resistance: Policy Recommendations to Save Lives." Retrieved on August 21, 2012, from http://www.idsociety.org/IDSA/Site_Map/Policy___Advocacy/Antimicrobial_Resistance/Strengthening_U_S_Efforts/Statements/Combating_Antimicrobial_Resistance___Policy_Recommendations_to_Save_Lives.aspx.

pediatric patients, immunocompromised patients, and combat veterans.³ The unique interaction between adaptable pathogens and the challenge of developing safe and effective treatments in a timely manner underlines the importance of exploring potential alternative development and regulatory pathways.

Current Efforts to Address Issues in Antibacterial Drug Development

Brookings Expert Workshop on Facilitating Antibacterial Drug Development

The Engelberg Center for Health Care Reform at Brookings held an expert workshop on May 9, 2012, to discuss methodological and regulatory challenges inherent in antibacterial drug discovery and to explore possible solutions to make the process more efficient. Convened in cooperation with the U.S. Food and Drug Administration (FDA), the workshop incorporated a broad range of perspectives including patients, providers, developers, regulators, academic researchers, and others with a vested interest in antibacterial drug development. Several key areas of action were identified through the discussions.

Examining Benefit-Risk Considerations

The need to reevaluate acceptable levels of risk and benefit in new treatments was proposed as an important next step in addressing unmet need for antibacterial drugs. Participants noted that striking an appropriate balance between the regulatory requirements for the approval of new antibacterial products and understanding clinicians' and patients' willingness to accept varying levels of uncertainty regarding potential risks is difficult, but that opportunities also exist for making the development and regulatory processes more efficient and predictable.

Harnessing Novel Statistical and Methodological Approaches

Experts at the workshop recommended exploring the use of various statistical and methodological tools to make clinical trials more efficient. This could include application of natural history studies, pharmacokinetic and pharmacodynamic analysis, Bayesian methods, and tiered trial designs that reduce the number of patients required in trial phases. All these options will require additional examination by experts to ensure their capacity to improve drug development and appropriately address clinical needs.

Streamlining the Clinical Trials Process

Participants proposed many opportunities to make the administration of clinical trials more efficient and less burdensome. The need to develop and apply rapid diagnostic tests in order to facilitate patient enrollment into trials was one area highlighted in the discussion. Another issue put forward in the workshop centered on reducing the amount of non-clinically meaningful data collected as part of trials. Experts suggested that this would help to reduce the costs and data management needs associated with large trials. They also proposed the creation and maintenance of a clinical trials network capable of providing an established infrastructure for new antibacterial drug trials. Such a network could assist in reducing start-up costs and more efficient ramp-up of clinical investigations.

Prioritizing Unmet Need

Participants suggested that areas in need of immediate focus could be identified and agreed upon by a broad group of stakeholders. A possible means to accomplish this could include creating a clear and predictable development pathway for areas in which there is an identified unmet medical need that could be specific to a disease area or multi-drug resistant organisms. This identification would enable stakeholders to solicit broad support and increased resources for encouraging development.

³ Pew Health Group. (2011). "Reviving the Pipeline of Life-Saving Antibiotics: Exploring Solutions to Spur Innovation." Retrieved August 21, 2012, from http://www.pewhealth.org/uploadedFiles/PHG/Content_Level_Pages/Issue_Briefs/AIP_PipelineProceedings_9_web.pdf.

Mobilizing an Advocacy Network

Participants suggested that issues of antibacterial drug development and multi-drug resistance could benefit from the efforts of advocacy organizations. They also noted that issues facing antibacterial development and resistance could be more broadly understood through increased communication with patient communities and increased engagement of all stakeholders.

Limiting Use

Experts recommended increased outreach to health care professionals and relevant societies in order to promote proper antibacterial stewardship. New antibacterial drugs will likely be developed for narrower or pathogen-specific indications in the future. Participants noted that efforts to introduce new antibacterial products need to include increased awareness and understanding of their appropriate clinical use.

In all, the expert workshop presented FDA and stakeholders with an important first step in outlining drug development and policy initiatives that will be critical to improving antibacterial drug discovery and development.

Task Force for Antibacterial Drug Development

FDA's Center for Drug Evaluation and Research (CDER) announced the formation of an antibacterial drug development task force at the Brookings expert meeting on May 9. The task force consists of CDER staff representing various offices within the Center and will focus on facilitating antibacterial drug development through a broad collaboration of stakeholders.

Brookings Council on Antibacterial Drug Development

In order to further the work described above, the Engelberg Center has been asked to convene the Brookings Council for Antibacterial Drug Development (BCADD) under a cooperative agreement with FDA. BCADD will primarily meet to provide insights on specific scientific and policy topics related to facilitating antibacterial drug development. The goal of BCADD meetings will be to facilitate discussion among a broad range of thought leaders with expertise in fields such as public health policy, clinical practice, patient advocacy, statistics, and antibacterial drug development. Individuals directly involved with FDA's internal Task Force for Antibacterial Drug Development and experts working on related projects not funded by FDA will participate in the council. Council members will be asked to identify and discuss high-level issues where action is needed by each stakeholder group over the next one to two years for successful promotion of antibacterial drug development.

Clinical Trials Transformation Initiative

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership comprised of more than 60 organizations from across the clinical trial enterprise. On August 20, 2012, CTTI convened a meeting of experts to address several of the statistical and methodological challenges in antibacterial drug development including non-inferiority trial designs, determination of non-inferiority margins, and use of pre-clinical data and data on historical controls in designing confirmatory studies.

Workshop Scope and Objectives

The first half of the workshop will focus on the work that has been done by FDA's Antibacterial Drug Development Task Force, Brookings, and CTTI to date. The morning's kick-off will also serve as an introduction to BCADD. This will be followed by discussion on statistical and methodological issues in antibacterial drug development and benefit-risk considerations. Discussion will be focused on these issues in order to flesh out actionable next steps for furthering work in the specified areas.

Sessions I and II: Statistical Challenges in Antibacterial Drug Development

Session I will update BCADD participants on outcomes from the CTTI meeting on August 20. The discussion surrounding specific proposals for innovative trial designs and data analysis introduced at the meeting will be summarized for BCADD. Session II will focus on seeking input from BCADD participants on CTTI meeting outcomes. The scientific merit of the various proposals coming out of the CTTI meeting and feasibility of implementing those proposals agreed to be worth pursuing will be discussed.

Session III: Benefit-Risk Considerations

Risks are associated with all medical interventions, and it is essential to fully understand and carefully weigh the benefit-risk profile of a product before it is approved for the market. The role of regulators is to weigh the potential benefits of a product against the potential risks in order to ensure that safe and effective treatments are available. A wide array of data is collected by both product developers and regulators. Clinical trial data and outcomes, the underlying characteristics of the target disease, comparison to other drug products or standard of care, and the needs of particular types of patients are factored in the decision to move a drug forward through trials and/or to seek approval for patient use.

Varying frameworks can be used to evaluate the benefit-risk profile of a product, with different weight accorded to each contributing factor. In an effort to address differences of opinion on how to approach benefit-risk and provide greater clarity on FDA processes, the Food and Drug Administration Safety and Innovation Act of July 2012 directed FDA to establish a cohesive risk-benefit assessment framework. The development of the framework is part of a five-year plan that includes public workshops, opportunities to solicit feedback on the proposed framework from stakeholder groups, and forums to solicit patient perspectives on benefit-risk assessment in drug development. A recent example of how FDA is engaging patients in order to inform benefit-risk considerations was the Patient Network Annual Meeting held on May 18, 2012, through the Office of Special Health Issues in collaboration with CDER, the Center for Biologics Research and Evaluation, and the Center for Devices and Radiological Health. The goals of the meeting were to better understand patient views of perceived benefits and risks related to medical products. The topics included the drug and medical device regulatory processes and practical approaches to collecting meaningful patient input.

Given the unique challenges and special populations involved in antibacterial drug development, a revised benefit-risk framework may be especially relevant in exploring innovative drug development pathways. Considering ways to incorporate all data about a product in such analyses, so as to expedite development, is particularly important. Economic and development challenges in antibacterial drug discovery provide added incentive to maximize the efficiency of the trials process. In a setting where therapeutic options to treat patients are lacking (e.g., patients suffering from serious or multi-drug resistant infections), patients and health care providers may have to accept a higher level of uncertainty or risks associated with new treatment, given the lack of other satisfactory treatment options. Where on the spectrum of risk uncertainty should a treatment be in order to gain approval? What are the implications of this spectrum for drug safety and access? How can stakeholders work to better inform patients about the tradeoffs inherent in balancing risk and benefit? Session III will explore these issues and outline constructive, actionable next steps to further a dialogue on benefit-risk considerations and their impact on antibacterial drug development.