ENGELBERG CENTER for Health Care Reform at BROOKINGS

August 30, 2012

Meeting Summary

Brookings Council on Antibacterial Drug Development Kick-Off Meeting

Introduction and Background

Antibacterial drug development in the United States was robust in the latter part of the 20th century with landmark development and approval of antibacterial products to treat a wide range of infectious diseases. However, starting around 2000, there was a decline in the development of new antibacterial drugs. The factors that initially contributed to this decline likely included the saturation of the market with products to treat current strains of susceptible pathogens and shifts in the pharmaceutical industry towards more lucrative areas of research. Additional factors impacting the field of antibacterial drug development that arose in subsequent years included an increased concern from public and government sectors regarding (1) antibacterial drug safety issues and the appropriate balancing of risks and benefits for antibacterial drugs, (2) reliance upon clinical trial designs to evaluate new antibacterial drugs that lacked scientific validity and lacked the capacity to assess benefit, particularly for less serious bacterial infections, and (3) clinical trial data integrity issues.

Controversy over the clinical trial data and approval of the antibiotic Ketek (*telithromycin*) in 2006 and 2007, for instance, demonstrated the issues surrounding clinical trial design concerns, antibacterial drug safety, and data integrity issues to the public at large and spurred intense debate.[1] As a result of these concerns regarding the scientific validity of clinical trial designs to assess efficacy and balance risks and benefits, the U.S. Food and Drug Administration (FDA) began to ask for additional information in its consideration of antibacterial drug applications. While addressing these requirements would yield more information about the safety profiles of the products prior to entering the market, they also increased the cost of trials and slowed the development process, reducing the sponsor's potential return on investment. As industry saw profits plateau, the field of antibacterial drug development became less attractive, and companies continued to scale back development programs in this area.

In parallel, there has been a steady increase in the incidence of serious bacterial infections with pathogens resistant to available treatment options. A variety of social, clinical and systematic factors have accelerated the emergence of resistant pathogens. The relatively low cost of antibacterial drugs, and public misconceptions about the products' safety, has contributed to their widespread and sometimes inappropriate use. The convergence of decreased antibacterial drug development and the increased incidence of drug resistant-pathogens have created a public health crisis with significant short and long term implications.

A coordinated effort by all stakeholders will be essential to identify, develop, and implement a holistic set of solutions to address the challenges of antibacterial drug development. Legislative action, regulatory rule-making, venture capital strategies, advancements in basic, translational and

[1] Harris, G. (2006, July 19). *Approval of Antibiotic Worried Safety Officials*. The New York Times. Retrieved February 20, 2013, from http://www.nytimes.com/2006/07/19/health/19fda.html?_r=0.

methodological research, and other innovative measures should be considered. There are already a variety of efforts underway to address some of these obstacles. FDA's Center for Drug Evaluation and Research (CDER) has formed a multidisciplinary Antibacterial Drug Development Task Force to identify mechanisms to facilitate antibacterial drug development (e.g., revising guidance documents, exploring novel development pathways and methodologies, etc.). The Task Force includes staff from a number of groups within the Center, including the Offices of Antimicrobial Products, Anti-Infective Drugs, Medical Policy, Biostatistics, and Clinical Pharmacology, to facilitate broad-based solutions.

Other federal efforts include the government-wide Interagency Task Force on Antimicrobial Resistance. Task force membership includes cross-cutting representation from government agencies with a vested interest in antibacterial use, including the FDA, National Institutes of Health, Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, U.S. Department of Agriculture, Department of Veterans Affairs, Department of Defense, Environmental Protection Agency, Agency for Healthcare Research and Quality, Health Resources and Services Administration, and the Health and Human Services Offices of the Assistant Secretaries for Health and Preparedness and Response. The Task Force developed an action plan in 2001, last updated in 2012, that outlines "specific, coordinated federal actions" to combat resistance, such as improving the detection and monitoring of resistant infections and strengthening coordinated basic research on resistant pathogens.[2]

Congress has also sought to address this issue and passed the Generating Antibiotic Incentives Now (GAIN) Act in the summer of 2012. The Act provides extended market exclusivity for certain antibacterial drug products granted the GAIN designation and FDA approval.

Outside of government, there are several groups that are also working in this field. The Infectious Diseases Society of America (IDSA) represents physicians, scientists, and other health care professionals who specialize in infectious diseases. IDSA has developed a number of proposals addressing various aspects of the antibacterial drug development process, including one proposing a Limited Population Antibacterial Drug (LPAD) designation. LPAD represents a novel regulatory approval pathway focused on the development of antibacterial drugs for patient subgroups with serious infections and limited or no therapeutic options (i.e., areas of unmet medical need). Like any other antibacterial drug product, use of products approved through this pathway would need to be appropriately stewarded. Additional attention would be needed to ensure that the products were used to treat the specified indications or patient subgroups, since the risks of such drugs would be less well characterized than those studied in a broader patient population.

Other initiatives include those by the Foundation for the National Institutes of Health (FNIH) and the Clinical Trials Transformation Initiative (CTTI), both public-private partnerships, to explore methodological issues, such as the development of well-defined and reliable endpoints for antibacterial clinical trials. Finally, the Engelberg Center for Health Care Reform at Brookings formed the Brookings Council on Antibacterial Drug Development (BCADD) as a collaborative forum for thought leaders to identify actionable next steps in this field and seek broad stakeholder engagement. BCADD work is convened in cooperation with FDA. Together, these initiatives aim to establish a unique, collaborative environment in which stakeholders can coordinate and build upon each other's work to promote antibacterial drug development for patients in need.

[2] Centers for Disease Control and Prevention. (2012). *Interagency Task Force on Antimicrobial Resistance*. Retrieved July 23, 2013, from http://www.cdc.gov/drugresistance/actionplan/taskforce.html.

Brookings Council on Antibacterial Drug Development Kick-Off Meeting

Under a cooperative agreement with FDA, the Engelberg Center convened the first meeting of BCADD on August 30, 2012. The meeting of the Council included an update on FDA's work to support antibacterial drug development, a presentation on potential improvements in clinical trial design and implementation, and an overview of FDA's risk-benefit framework. Council members were asked to identify key areas where BCADD might focus its efforts to address this public health problem. They were encouraged to consider collaborative, transparent, and innovative next steps that involve a broad group of potential stakeholders such as the government, industry, clinical community, and public.

Clinical Trials Improvements

The Clinical Trials Transformation Initiative (CTTI) convened a statistics think tank meeting at Duke University on August 20, 2012 focused on innovative approaches to the design and analysis of clinical trials in antibacterial drug development. The think tank included statisticians from academia, industry, and government. While CTTI's think tank did not develop specific proposals, the meeting identified various options to consider as potential next steps. An overview of some of the critical issues that emerged from CTTI's think tank were presented and discussed at the BCADD kick-off meeting. The BCADD discussion included the following topics: the use of a single study to provide confirmatory evidence, statistical challenges in non-inferiority trials, the potential for designing trials that compile data from patients with different body sites of infection, and a re-examination of the role and effect of prior antibacterial treatment in the design of non-inferiority clinical trials.

One-study Confirmatory Evidence

In assessing the appropriateness of a single study to provide confirmatory evidence as a basis for approval, it is important to consider what study attributes would be needed and what types of supporting evidence should be required. Generally, it is desirable to have at least two confirmatory studies that produce similar results to provide more confidence that the outcome of the trial can be replicated. In the absence of additional confirmatory studies, ensuring that trials are well designed and adequately controlled is especially important. It was generally agreed that when a development program is based around a single trial, that trial should be large, well-powered, and include strong representation of patient subgroups.[3] When a single trial is being used to establish product safety and efficacy, it is especially important to enroll patients from a variety of clinical sites to ensure a highly representative patient population. The trial could have fewer patients per site rather than a smaller number of sites with more patients to further enhance generalizability. Ensuring the quality of a single submission trial is always important but can be more of a challenge for non-inferiority trials. In a non-inferiority trial, potential problems with how the trial is conducted could bias the results toward demonstrating similarity between the two antibacterial drugs. Additional exploration of the supportive evidence is needed to bolster a single trial paradigm for antibacterial drug development.

Participants noted that it may be possible to include additional sources of information as supporting evidence for a single confirmatory study of an antibacterial drug product. There are several rich sources of information that could potentially be used as supportive evidence, including *in vitro* efficacy data, pharmacologic and exposure response data from animal models, and Phase II results in humans. Participants noted opportunities to explore potential similarities with the process for medical device

[3] The FDA's *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (1998) describes when one trial might, along with supportive information, provide evidence of effectiveness including the attributes of the single trial. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf.

approval, which often relies on non-clinical sources of information to demonstrate the product's mechanism of action. It may be possible to use laboratory-based data to demonstrate proof of concept for an antibacterial drug product's mechanisms of action against bacterial pathogens, in addition to supplying clinical data on the product's safety and efficacy.

Non-inferiority Trials

Many questions surrounding non-inferiority trials were discussed, including how clinical trial data from non-inferiority trials can more efficiently address evidentiary standards and how best to evaluate efficacy data derived from smaller trial populations. In addition, the following three central questions on non-inferiority trials were explored at the meeting:

- What can be done if there are no historical data to set the non-inferiority margin?
- If trials are small, what can be done to make the analysis more efficient?
- Are there analytic approaches that could appropriately weigh evidence to assess drug effect from patients with infections at different body sites?

Several innovative trial designs have been proposed for non-inferiority studies of antibacterial drug products where there is not sufficient historical data to set inferiority margins. A three-armed trial including the test treatment, an active control, and a placebo is a design option that could remove the need to rely on potentially unreliable historical data. However, such an approach would require the quick administration of rescue treatments for patients in the placebo arm, and could be clinically inappropriate in some instances (i.e., infections other than mild infections).

Endpoints for non-inferiority trials also need to be examined if product developers are to realize further efficiencies in the trials process. Absent historical data on meaningfully-defined clinical cure, methods to develop a bridge between known margins (e.g., mortality) and clinical response need to be explored.

In addition to exploring endpoints, consideration should be given to acceptable ways to increase the efficiency of clinical trials through Bayesian methodologies for statistical analysis. By incorporating a Bayesian approach, it could be possible to increase efficiency to the point where trials can enroll significantly smaller sample sizes, which could make antibacterial clinical development more attractive. In particular, better use of historical information about the comparator drug in a non-inferiority trial as well as information from pre-clinical or early phase clinical studies through the application of Bayesian methods in the confirmatory trial appear to be a promising approach. However, the use of Bayesian methods in antibacterial development programs still has many aspects that must be better defined and fleshed out. Several participants noted that the use of Bayesian approaches to drug development could achieve more efficiency, but expressed concern that they should not be seen as a panacea for creating more efficient trials.

A number of proposals to link trial design and regulatory review have been put forward in recent years to facilitate and accelerate drug development and approval and to allow for more innovative drug development approaches, especially for therapeutic areas that are more difficult to study. These proposals include mechanisms that grant approval of products for targeted populations or specific pathogens and also seek to restrict use of the drug through labeling (e.g., IDSA's LPAD proposal). BCADD members suggested another design that could be built around smaller separate trials focused more on efficacy; through enrollment of smaller populations and use of novel statistical methods, this type of trial design could be coupled with downstream efforts to address safety such as Phase IV confirmatory studies. Participants also noted that smaller clinical trials could lead to an approval that adds boxed

warnings[4] to labels until a more robust safety profile is established. It was also suggested that the European Medicines Agency's (EMA) practices and guidance documents could help contribute to ideas about how to implement innovative trial designs and regulatory approval pathways.

BCADD meeting participants were supportive of efforts to explore all of the options presented and noted that any changes to the process should be focused on how to harness innovative methodologies and approaches to create a *smarter* process that ensures approved products are both safe and effective.

Improving Clinical Trial Logistics

While there was widespread agreement that rethinking the statistical and methodological approaches used in antibacterial clinical trials is very important, members of BCADD also cited the pressing need for process and logistical changes. The creation of clinical trials networks, for example, could result in more rapid trial execution. In a network, a standing infrastructure of clinical sites, providers, and researchers is established to facilitate trial startup and implementation for studying new antibacterial drugs. These networks could remove the need to "start from scratch" with each clinical trial, and would allow researchers to utilize an established system to initiate trials on a rolling basis and alleviate administrative barriers to ramping up an individual study. Similar networks have been successful in increasing the efficiency of clinical trials in other disease areas or patient populations, such as the National Institute of Allergy and Infectious Diseases' HIV/AIDS Clinical Trials Networks or the National Institute of Child Health and Human Development's Pediatric Clinical Trials Network.

Another area where participants thought there could be improvements to the clinical trial process was in patient recruitment. When patients present with serious or life-threatening infections, they must be treated as quickly. To be enrolled in a clinical trial, they must similarly be examined, given an initial diagnosis, and undergo a battery of confirmatory tests, but there may be additional requirements that can delay enrollment and treatment. The patient must be led through informed consent documentation, may undergo additional laboratory tests to measure inclusion or exclusion criteria for a particular trial, and have a range of clinical data taken down for trial records. Informed consent is essential but participants felt improvements to the current process are needed. Participants pointed out that this is a lengthy process, even when carried out at top speed. Critical bottlenecks in the recruitment process should therefore be identified and streamlined. Participants noted that there is a need for researchers, institutional review boards, and regulators to evaluate and simplify the consent process. Streamlining the forms would decrease the time providers must spend explaining paperwork and legal documents to patients and their families. Members also noted that a critical tool in improving the enrollment of patients into clinical trials and in treating them outside a trial setting was the development of fast, accurate diagnostics to reliably identify the infection and ensure that patients are given the most appropriate treatments.

Stewardship and the Societal Compact

As stakeholders pursue clinical trials improvements, it is also important to explore mechanisms to steward antibacterial drug products in order to preserve the products' efficacy. Addressing the relationship between increasing multi-drug resistance in pathogens and overuse in the clinical setting will be a significant part of a holistic approach to decelerating resistance, and could help shape product development. As noted earlier, there are proposals for mechanisms that could better target product use

[4] U.S. Food and Drug Administration. (2011). *Guidance for industry: Warnings and precautions, contraindications, and boxed warning sections of labeling for human prescription drug and biological products—content and format*. Retrieved from http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf.

through narrower indications in order to conserve the effectiveness of new antibacterial drug products approved through a limited use approval pathway. BCADD members also put forward a wide range of other proposals focused on changes to clinical care and public perception. Participants suggested initiatives utilizing public relations and education campaigns to inform the public about the dangers of overuse, as well as provider outreach and engagement efforts on issues of stewardship.

Better Understanding of Risk-Benefit Profiles

Representatives from FDA presented to the participants a structured assessment framework which is intended to both evaluate and communicate risk-benefit findings in regulatory decision-making. The agency is taking steps to further improve this risk-benefit assessment process by working toward a more structured framework. This will include a detailed five-year plan for development of a risk-benefit toolkit as well as public workshops to engage stakeholder communities in discussion around the impact of the risk-benefit framework.

Improving understanding of the risk-benefit framework will be especially important for antibacterial drug development, as there are often complex trade-offs in balancing patients' needs with potential risks. On one end of the risk-benefit spectrum are drugs with precise, well-characterized risk-benefit profiles. However, this reliance on precision may hamper innovative drug development and result in fewer new drugs on the market. The other end of the risk-benefit spectrum includes drugs that are less well-characterized with greater uncertainty surrounding their safety. While more drugs might make it to market under these conditions, their risk-benefit profiles would lack precision. Finding the balance between these scenarios and pursuing it through efficient clinical trials and regulatory review will necessitate a constructive, open dialogue between all stakeholders in the health care setting.

BCADD members supported efforts to incorporate patient perspectives in conversations about acceptable risk-benefit in antibacterial drug development, such as the degree of risk patients are willing to accept and how factors like unmet need influence these decisions. Participants agreed that the framework of the proposed risk-benefit matrix was an essential tool to better understand the risk-benefit profiles for antibacterial products, particularly those for treating patients with serious or life-threatening infections. Through public awareness campaigns and feedback from patient communities, both sponsors and regulators will be better equipped to make decisions on the balance of risk and benefit and to understand where patient tolerance of potential adverse events or uncertainty is impacting drug development.

Economic Factors Effecting Development

Over the course of discussion, several economic issues that impact the development of antibacterial drugs were noted by participants. Many of these issues are interrelated, and progress in one area may hinder efforts in others. A critical example of this is the potential for stewardship efforts to decrease investment in development. Stewardship initiatives designed to achieve prudent use of antibacterial drug products, which can slow the rate at which resistance develops to antibacterial drug products, may also potentially limit the return on investment industry can anticipate for that product. Participants cited the need to consider alternative reimbursement structures that could support appropriate stewardship and increased investment, putting forward the traditionally high reimbursement rates for cancer treatment as one example of a payment structure capable of having a positive impact on development and also potentially fostering more appropriate and conservative use. There were concerns about the public health impact of this particular model, however, particularly given the current climate of cost concerns in health care.

It was also noted that an evaluation of the increased cost of care due to the burden of resistant pathogens would be useful in better understanding the societal and economic costs of having fewer treatment options. Participants pointed out that it would also be important to understand the potential impact of narrower indications or more limited development programs on insurance coverage for these products. Changes such as restrictive labeling and increased costs could hinder the inclusion of products into formularies. Participants suggested engaging payers in the discussion about potential alternative reimbursement policies for antibacterial drugs.

The role of economic incentives to spur industry investment in antibacterial drug development will also need to be explored. BCADD members cited the GAIN Act, passed in summer 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA), as an example of an economic policy lever used to boost drug development. The GAIN Act increases the period of market exclusivity and grants priority review for products that receive a designation as a Qualified Infectious Disease Product under the Act. Shortened time for regulatory review and a longer period of market exclusivity is expected to be a powerful economic incentive. While it is too early to see the effects of the GAIN Act on drug development, participants felt that it is an important step toward creating further policies that help to encourage developers to invest in development of antibacterial drug products.

Infrastructure Development

Finally, many participants expressed concern about maintaining and expanding the infrastructure necessary to support antibacterial drug development. This was especially true for issues such as educating and retaining a new generation of dedicated researchers. BCADD members hope that stakeholders will be able to identify ways to encourage the creation of rigorous training or fellowship programs to help create greater numbers of infectious disease experts and clinical trialists capable of improving the drug development paradigm. Some specifically noted that education and fellowship programs could potentially be facilitated by the National Institutes of Health through either expanding existing or creating new programs.

Similarly, members noted that finding mechanisms or processes to better support investigators, grant applicants, and drug sponsors as they navigate discovery, development, and regulatory review will be important to ensure as smooth a development process as possible. Participants also discussed the potential for pre-competitive data and resource pooling as a way to further bolster the development process and potentially increase collaborative innovation.

Next Steps

Based on the discussion at the August 2012 kick-off meeting of the BCADD, it is clear that there are a variety of interrelated and complex factors that impact the development of new antibacterial drug products. In order to pursue solutions, the Engelberg Center will create ad hoc working groups to further explore the following topic areas: economic factors, stewardship and the societal compact, clinical trial improvement, and supporting the drug development infrastructure. Given the need to stimulate efforts in economic factors, stewardship, and social compact initiatives, BCADD will prioritize the formation of these working groups. By organizing the efforts of the council within a set of specific topics, the Engelberg Center hopes to support the identification and refinement of concrete, actionable steps that can be implemented across stakeholder groups – manufacturers, government, and the broader health care community – to overcome critical obstacles in antibacterial drug development and preservation.