

Facilitating Antibacterial Drug Development

Origins of the Current Public Health Crisis of Antibacterial Resistance

Antibacterial drugs play a critical role in the ability to cure infectious diseases and improve public health. However, widespread emergence of resistant pathogens renders current treatments less effective, creating unmet medical needs for patients with serious resistant infections and presenting a significant public health threat. Resistance develops due to a combination of factors, including natural factors (e.g., genetic mutations, selective pressure) and social factors such as over-prescribing and inappropriate use (e.g., poor medication adherence and persistence). Recognizing the urgent and growing problem of antibacterial resistance, efforts across the health care system are focusing on preserving the effectiveness of existing antibacterial drugs by attempting to promote the effective use of existing antibacterial drugs. The problem of resistance stemming from antibacterial drug overuse is global. Antibacterial drugs are more readily accessed without a prescription and often over-prescribed in other parts of the world.

While efforts to combat resistance and encourage prudent use are critically important, failure to simultaneously respond with development of new antibacterial drugs to replace existing, less effective therapies, will fall short of an adequate response to this public health challenge. The antibacterial research and development pipeline has slowed dramatically, with only a few large pharmaceutical companies supporting antibacterial drug discovery programs, and relatively few new antimicrobial drugs and new classes of drugs introduced in recent decades. An Infectious Diseases Society of America (IDSA) analysis conducted in 2004, for instance, 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 2012.¹ Medical product developers have been shifting resources away from developing new antibacterial drugs. This is due, in part, to uncertainty and concerns about the regulation and reimbursement for antimicrobial drugs. For example, antibacterial drugs are typically used episodically and for a short duration, which limits the volume of use and economic incentives for a manufacturer to develop and market antibacterial products. This is in contrast to drug therapies for chronic conditions that can generate higher returns through volume with more stable and predictable patient populations. Some express the view that the U.S. Food and Drug Administration (FDA) has adopted a more conservative stance on its approval standards for antibacterial drugs in recent years, further compounding cost considerations and making the development of antibacterial drugs less financially attractive. In contrast, others hold the view that clinical trials conducted in the past lacked a sound scientific foundation to appropriately evaluate efficacy and that changes to the approaches used to study antibacterial drugs were necessary.

¹ 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.

Lack of current investment in research and development in this field is expected to have further negative implications on the availability of new antibacterial drugs in the future. Given the approximate seven to 12 year lag between drug discovery and marketing, even with a jumpstart in development, it would be years before new antibacterial drugs reach the market. In order to address the public health crisis, immediate investment in antibacterial drug research and development will need to be coupled with a reexamination of the current antibacterial drug development paradigm to identify opportunities for improvements that will speed patient access to valuable new drugs.

Meeting Objectives and Scope

On May 9, 2012, the Engelberg Center for Health Care Reform at Brookings convened the “Facilitating Antibacterial Drug Development” expert workshop to explore solutions to methodological and regulatory challenges that can make the antibacterial drug development process more efficient. While economic factors may also influence this process, these factors were not the focus of discussion at this workshop. Specific workshop objectives included exploring the following:

- Existing paradigms for antibacterial drug development;
- Novel approaches to further antibacterial drug development, including use of pharmacokinetics and pharmacodynamics, Bayesian methods, innovative clinical trial designs, new data sources, alternate clinical endpoints, and new regulatory tools; and
- Short- and long-term opportunities to advance the antibacterial drug development enterprise, through collaboration among stakeholders, improved regulatory science, and other means.

This meeting brought together a diverse set of stakeholders from both public and private sectors, including U.S. and European government agencies, academic institutions, medical product developers, and patient advocacy organizations. The discussion focused on productive exchange of ideas, development of a list of practical next steps for promoting antibacterial drug development, and possible roles and responsibilities for implementing these steps. During the meeting, participants suggested a number of broad principles and more actionable and concrete next steps. This document highlights these discussion points.

Need for an Improved Antibacterial Drug Development Paradigm

Workshop participants indicated that future antibacterial drug development should be facilitated by a clearer and more transparent development pathway for these drugs. Participants suggested that any paradigm shift in antibacterial drug development would need to consider the uncertainty of a drug’s safety and efficacy profile and recognize that an appropriate balance would need to be struck between weighing risk, benefit, and uncertainty and the availability (or lack of availability) of new antibacterial drug products. FDA’s Center for Drug Evaluation and Research (CDER) acknowledged these issues, reflected in its formation of an antibacterial drug development task force that will focus on facilitating antibacterial drug development through a broad collaboration of stakeholders.

Meeting participants noted a number of principles that could move the existing antibacterial drug development paradigm toward a more predictable and sustainable model. Participants also noted that these broad suggestions, which are briefly outlined below, will require significantly more consideration for their appropriate implementation.

Reevaluating acceptable levels of uncertainty

Participants noted that it would be important to reevaluate acceptable levels of uncertainty, particularly for patients who lack satisfactory treatment options (e.g., because of infections with multi-drug resistant organisms). While it is important for all new products to balance acceptable risk with demonstrated

benefit, meeting participants also acknowledged that in therapeutic areas without suitable treatment alternatives, such as multi-drug resistant infections, patients and their clinicians may be willing to accept more uncertainty regarding potential risks in order to avoid delayed access to new treatments.

Ensuring statistically rigorous and meaningful results from clinical trials

Stakeholders should consider how to ensure that clinical trial designs yield both statistically rigorous and clinically meaningful results. To date, challenges in determining appropriate non-inferiority margins have been one of the primary areas of questions about clinical trial design. However, participants emphasized that it is equally important to ensure that the information from these trials is clinically relevant. A well-designed clinical trial may allow developers and regulators to assess efficacy but may not answer all of the questions that parties would like to know for real-world clinical practice. For example, patients who receive the drug in real-world clinical practice are likely to be sicker, have a greater number of co-morbid conditions, and receive a wider range of drug therapies than the clinical trial population.

Evaluate the role of rapid diagnostic tests

Previous discussions on the topic of antibacterial drug development have noted that a lack of rapid and accurate diagnostic tests has created challenges to enrolling patients with the target pathogen into clinical trials. During this meeting, participants reiterated that more efficient clinical trial enrollment could be achieved with new diagnostics that can rapidly identify infections. However, some participants pointed out that these diagnostics will most likely be considered experimental (i.e., intended only to screen patients for clinical trials and will not have been FDA approved nor included in the product label), and thus questioned their utility for use in clinical practice and the clinical relevance of trial results based on a population of patients selected using these diagnostic tools.

Identify challenges that are specific to clinical trials for antibacterial drug development

Clinical trial science is still developing and evolving. Given that many of the challenges faced by the antibacterial drug development enterprise are common to other therapeutic areas, infectious disease researchers could collaborate with those in other fields to more generally advance clinical trial science. However, antibacterial drugs also present some unique challenges that should be addressed separately from general clinical trial issues. Data collection presents one such challenge. Participants noted that large amounts of data are collected from patients, which drives up the cost of conducting these trials. However, much of the data collected seem to provide little value in understanding the performance and safety of new antibacterial drugs. Along with FDA, participants suggested that researchers could reevaluate what pieces of information are essential to collect in order to make clinical trials more efficient.

Consider use of other sources of information

Meeting participants noted that while clinical trial data have been, and will continue to be, an important source of information, other sources of data can also inform researchers about a product's safety and efficacy profile. These sources include natural history studies and pharmacodynamics and pharmacokinetics studies obtained from animal models. Bayesian methods may also play an important role in determining how to use this data to inform clinical trial design.

Potential Next Steps

Meeting participants also discussed a number of potential next steps that could help to advance the antibacterial drug development paradigm.

Prioritization of unmet need

Developing viable treatment options for patients infected with organisms resistant to available therapies must be addressed to remedy the current public health problem. In addition, reviving the antibacterial drug pipeline to create ongoing development of new antibacterial products is a longer-term necessity, and the existing development of new options could help to avoid situations where there is unmet need. Participants suggested first identifying and agreeing upon areas of immediate unmet need and focusing current efforts on these areas. This could include creating development pathways that provide a clearly defined balance between feasibility issues and level of uncertainty and fall within an acceptable regulatory approach to evaluate safety and efficacy. Also, a development pathway may be specific to certain areas such as treatments for patients with infections for which satisfactory treatment options are lacking. Prioritization could help to efficiently allocate resources while garnering broad stakeholder support for these needed changes.

Tiered development for antibacterial drugs targeting areas of unmet need

Meeting participants suggested a possible alternative development pathway for antibacterial products, termed “tier B” and “tier C.” In contrast to the current clinical trial paradigm, “tier A” (typically two large phase 3 clinical trials to demonstrate confirmatory evidence of efficacy) participants suggested that areas with high unmet needs could benefit from tier B and C’s use of smaller clinical trials that may merge results across multiple body sites and provide a more rapid means to study and, if successful, provide treatment options for patients where satisfactory treatment options are lacking.

Tier B development would be based on one large phase 3 study and one or more smaller studies. Participants thought that this may be suitable for the development of an antibacterial drug in an area of unmet need. For example, tier B development may consist of a large phase 3 study conducted in one body site (e.g., complicated intra-abdominal infections) to demonstrate general efficacy and a smaller open-label study to provide information on the drug’s performance in the targeted area of unmet need (e.g., treatment of patients with infections for which we lack satisfactory therapy.)

Tier C development would rely upon smaller studies. For example, tier C could include three small comparative and descriptive studies: the first would be a prospective, randomized, open-label study compared to best available therapy enrolling patients with infections at each of several different body sites (with a sample size of approximately a few hundred patients), the second would be an open-label study that would serve as a companion salvage study for the first study, and the third would be an observational study of an (inadvertently) ineffective therapy to estimate the placebo effect and serve as a reference point for the first prospective study.

Participants also cautioned, though, that by relying on smaller trials, tier B and C development carries a certain degree of risk, as they will be more susceptible to confounding and patient heterogeneity. Additionally, while tier B and C can demonstrate a product’s efficacy, they are less suited to demonstrate safety, and medical product developers may have to develop other ways to supplement safety information. To mitigate risk, the label could indicate that data are limited and should only be used when alternatives are not available or not appropriate therapeutic choices.

Development of a clinical trials network

Participants suggested that developing a clinical trials network could help to improve the efficiency of conducting infectious disease clinical trials of new antibacterial drugs. The development of the infrastructure to conduct trials could possibly facilitate clinical trial enrollment and help to overcome some of the challenges that are inherent to studying a new antibacterial drug. Ideally, this network

should have the capacity to “plug in” new antibacterial drugs to study efficacy and safety in a timely manner, reducing trial start-up burden. This network could also help to build a historical control dataset by collecting data on outcomes of ineffective therapies and help to facilitate more rapid enrollment of patients into infectious disease clinical trials soon after hospital admission. Participants suggested that this clinical trials network could target intensive-care units at hospitals and leverage lessons learned and infrastructure from existing networks, such as the Pediatric Trials Network or the HIV Vaccine Trials Network. This clinical trials network could be developed and supported through a public-private partnership.

Tools and mechanisms to limit use of antibacterial drugs on the market

Preserving the utility of existing and new products for as long as possible is critical. Meeting participants stressed the importance of developing and employing tools and mechanisms to promote effective use of antibacterial drugs once they are marketed. These may include approving drugs for narrower indications, encouraging the practitioner and payer communities to avoid broad off label use, and developing better evidence on determinants of patterns of use in clinical practice.

Mobilization of advocacy communities

Participants noted that bacterial infectious diseases have a less prominent and active patient advocacy community than is present in other disease areas. Helping to mobilize an advocacy community could emphasize the gravity of this public health problem and serve as a catalyst for research and development in this area. While the bacterial disease patient population is diverse, an appropriate advocacy community may include infectious disease physicians and immunosuppressed patients in other disease areas (e.g., cancer or HIV) for whom opportunistic infections pose a considerable concern. Infectious disease physicians, in particular, could play a valuable advocacy role for these patients since they face the direct impact of a lack of treatment options.

Conclusion

The increase in antibacterial drug resistance, coupled with a decrease in effective treatments, has created a public health crisis that will only worsen if not promptly addressed. Participants in this workshop identified a number of potential steps to advance the antibacterial drug development enterprise. Sustainable solutions will be complex and require collaboration among the entire stakeholder community, including both public and private entities. Participants stressed the importance of maintaining inclusiveness and maximizing transparency as these collaborations occur and appropriate solutions are adopted by the community. Given the urgency of the problem of antibiotic availability, steps like these should be undertaken as soon as possible.