ENGELBERG CENTER for Health Care Reform at BROOKINGS

Modernizing Antibacterial Drug Development and Promoting Stewardship

Meeting Summary
February 7, 2014

Introduction

Antibacterial drug resistance is a global public health threat with serious societal consequences. Drug-resistant infections currently cause more than 23,000 deaths annually in the U.S. and contribute significantly to morbidity and lost productivity.[1] Excess spending from resistant infections costs the U.S. health care system over $20 billion annually.[2] Drug resistance has accelerated because of inappropriate use of antibacterial drugs across health care settings, which has been enabled by volume-based reimbursement policies, low antibacterial drug prices, and skewed perceptions of drug safety and benefits. However, even with prudent use, the natural evolution of resistant pathogens will continue to threaten the efficacy of available therapies. Therefore, combating drug resistance will require catalyzing the development of innovative antibacterial drugs, in addition to measures to support appropriate use of all antibacterial products.

Unfortunately, a number of economic, scientific, and regulatory issues have complicated the development of novel therapies, leading to growing concerns about serious drug-resistant infections. Gram negative bacteria, in particular, have become a major public health threat as treatment options have dwindled, and no new therapeutic classes that target these organisms have been discovered since the 1960s.[3] This lack of innovation has led to calls by many stakeholders to reinvigorate the antibacterial drug pipeline by strengthening development incentives and frameworks.

On February 7, 2014, under a cooperative agreement with the U.S. Food and Drug Administration (FDA), the Engelberg Center for Health Care Reform at Brookings brought together major stakeholder groups to explore these challenges as well as potential solutions. Building on previous work aimed at facilitating antibacterial drug development through streamlined pathways, the morning's sessions were dedicated to discussion of the value of pathogen-focused approaches for stimulating innovation in areas of unmet medical need. Stakeholders provided their perspectives on proposed pathways for pathogen-focused drug development and discussed evidentiary requirements that could support the approval of pathogen-focused drugs. In the afternoon, participants worked to identify sustainable stewardship strategies for slowing the emergence of resistance to antibacterial drugs used in ambulatory care for less serious infections.

Defining Pathogen-Focused Drug Development Frameworks

Targeted approaches to antibacterial drug development – including for the most seriously ill patients or other patient subgroups with unmet needs – have been proposed as a potential mechanism for reducing trial costs and stimulating investment in this area of urgent public health need. Many feel that leaner pathogen-focused development programs could prove more attractive to drug sponsors, and the resulting indications could improve patient outcomes and better support stewardship aims. However, others have expressed concern that implementation of such development programs could compromise the rigor of existing drug safety and efficacy standards.

One of the main objectives of the morning's sessions was to consider how defining pathogen-focused frameworks could support innovation while maintaining rigorous evidentiary standards for regulatory approval. Workshop participants were asked to share their input on possible definitions for the term "pathogen-focused drugs," including the most narrow interpretation (drugs active versus a single species) and broader definitions (e.g., drugs active against a few species within a genus). Participants indicated that, generally, products active against a single species would be challenging to evaluate

because (1) researchers would reduce the population of patients eligible for study by focusing on one pathogen; and (2) studies involving one pathogen would necessitate rapid diagnostics capable of accurately identifying the pathogen of interest. In the case of very rare pathogens that affect few patients, it may also be necessary to pool data across infection sites, although the clinical rationale for doing so may vary by body site.

Stakeholders agreed that defining pathogen-focused drug development is important because it has implications for data collection and clinical trial designs. Regardless of how pathogen-focused frameworks are ultimately defined, participants stressed that FDA should consider the balance of a drug's benefits and risks in accordance with the seriousness of the public health threat, the availability of therapeutic alternatives, and the incidence of the pathogen (and thus the difficulty of conducting large clinical trials).Given the varying difficulty of conducting clinical trials and differences in experimental drugs' spectra of activity, participants noted that a flexible regulatory "umbrella" framework may be necessary to accommodate diverse approaches to pathogen-focused drug development.

Citing the example of the European Medicines Agency (EMA), which recently released an addendum[4] to its guidance on antibacterial drugs, participants reiterated the importance of flexibility and case-by-case assessment in regulatory decision-making and noted that an overly conservative approach could impair development efforts. In the U.S., draft guidance on antibacterial therapies for patients with unmet medical needs for the treatment of serious bacterial diseases was made available for comment in summer 2013.[5] However, meeting participants indicated that clearer guidance on acceptable therapeutic targets and evidentiary standards could incentivize investors and drug sponsors to enter the antibacterial drug market.

Workshop participants stressed that streamlined approaches would only be appropriate for serious infections (e.g., infections caused by pathogens identified as urgent threats[6]) where the benefits of an effective therapy would outweigh any risk associated with uncertainty resulting from smaller clinical datasets. Such infections would also need to be sufficiently rare to preclude traditional phase 3 development programs. However, there was less agreement around the concept of unmet need and what it should mean for ethical conduct of these trials. Some felt that it would be imprudent to wait until infections were resistant to all available therapies and that novel therapies should be evaluated for non-inferiority against a viable comparator, while others felt that streamlined development programs would only be appropriate for patients with no therapeutic alternatives. In cases in which patients had no therapeutic alternatives, it would be necessary to conduct superiority trials and potentially to use observational or historical data in place of a control arm. Some felt that superiority studies could be very valuable in the early stages of innovation, but that non-inferiority studies could be used later to study follow-on products (e.g., those with less toxicity, more convenient dosing, etc.).

Evidentiary Considerations to Support Pathogen-Focused Drug Development

Because the etiology of an infection is often unknown at enrollment, clinical drug development for antibacterial drugs has historically required large numbers of patients to generate adequate statistical power. However, large trials have driven up development costs and may expose patients with drug-resistant infections to unnecessary risk. In the absence of large clinical safety and efficacy databases, many participants agreed that preclinical and clinical pharmacology data could play an enhanced role in antibacterial drug development and evaluation.

A strong pharmacokinetic and pharmacodynamic (PK/PD) data package was identified as a key component of EMA's approach to regulatory decision-making in this field. As described by workshop presenters, indexing drug exposure to minimum inhibitory concentrations and using PK/PD exposure-response data to optimize dosing would be critical for designing a sound clinical development program. Some participants felt that using PK/PD data in this manner could help boost the odds of regulatory success and cited the strong positive relationship between the use of PK/PD target

attainment and later regulatory success. In contrast, others pointed to recent work[7] that failed to establish a relationship between the use of PK/PD-guided dosing and improvement on certain clinical endpoints.

A crucial aspect of antibacterial drug development is identifying valid clinical endpoints that are objective and predictive of clinical improvement and survival. Mortality has long been used as an endpoint in antibacterial drug trials, but many feel that there is room to establish clinical endpoints directly relevant to how patients "feel and function" following serious infections. Such endpoints would ideally be evaluated earlier in the course of a disease and be predictive of long-term survival. Participants mentioned that broad "clinical response" endpoints were often subject to clinician judgment and not predictive of long-term clinical benefit; in some cases, patients judged "cured" based on clinical response did not survive. Some suggested that adopting composite, hierarchical endpoints that evaluate subjects on multiple outcomes of interest (e.g., symptom resolution and survival) could be beneficial in evaluating antibacterial drug treatment effects. Participants noted that there is also a need to reevaluate the use of 30-day all-cause mortality as a trial endpoint because of the potential for confounding due to comorbidities. Recent work on hospital- and ventilator-acquired bacterial pneumonia (HABP/VABP) appears to support earlier evaluation of mortality (e.g., at 14 days) and has identified other clinical endpoints, such as oxygenation, that may be predictive and meaningful to patients and their care teams.[8]

Challenges in Pathogen-Focused Drug Development

Workshop participants cited a number of challenges confronting pathogen-focused drug development. Key among them was the need for rapid and accurate diagnostic technologies to support drug development and appropriate clinical use of pathogen-focused products. Traditional culture methods are too slow to allow for the widespread use of targeted therapies in patients with serious infections, and such patients often receive broad empiric therapy as a first-line intervention. In a clinical trial setting, participants noted that it would be very difficult to enroll the appropriate patient population in a timely manner (e.g., ideally before empiric therapy) without the existence of a relevant rapid diagnostic test, particularly for trials involving rare pathogens and drugs with a narrow spectrum of activity. Therefore, rapid and accurate identification of a pathogen and its susceptibilities will be critical for efficiently moving a targeted product through clinical development.

While diagnostic technologies have advanced rapidly in the last decade and increasingly use more sensitive and accurate DNA- and protein-based assays, they can be expensive and their use is not widespread. There is a need, in particular, for diagnostic tests for the drug-resistant gram negative pathogens that represent the greatest public health threat and key targets for pathogen-focused drug development. Participants noted that in some therapeutic areas, a sponsor has financed the development of a novel diagnostic to support clinical testing of their product, but this is less common in the infectious disease space and may not be a sustainable solution given the economic disincentives already affecting antibacterial drug development.

Antibacterial drugs are often used inappropriately, in part because the use of diagnostics is not incentivized even when they do exist. For example, despite the availability of a rapid test to detect the bacterium that causes about ten percent of pharyngitis cases, more than 50 percent of U.S. adults receive an unnecessary antibiotic prescription after visiting a primary care practice or emergency department for a sore throat.[9] This example is indicative of a larger problem with inappropriate use in clinical practice that must be addressed if pathogen-focused drugs are to be used in a limited manner. Drug resistance can develop quickly in settings with high levels of inappropriate use, which makes investing in products that must be used very judiciously an unattractive proposition for drug sponsors. Many fear that even if new pathogen-focused products are developed, resistance will rapidly follow without significant changes to reimbursement policies and medical practice.

Workshop participants also considered the importance of labeling for pathogen-focused drugs. Some noted that many physicians may not read or have access to drug labeling in the acute care setting, and that most are not well-versed in the drug regulatory process or accustomed to critically evaluating drug indications. Others stated that labels limit the extent to which products can be marketed, and that this could support appropriate use. Many raised concerns about effectively communicating to providers that pathogen-focused product approval may be supported by smaller safety datasets than products approved through traditional pathways.

Some participants proposed using Risk Evaluation and Mitigation Strategies (REMS) to enforce stewardship measures like use restrictions or registry requirements for pathogen-focused antibacterial drugs. However, in the absence of an identified serious safety issue, the rationale for limiting use through REMS may not be viable. Participants stressed that it would be important to monitor utilization patterns of these products as well as to promote effective postmarket safety surveillance.

Workshop participants identified payers and providers as necessary partners in promoting good stewardship practices and structuring incentives for antibacterial use. While many felt that pricing alone could not restrict use of novel antibacterial drugs since many physicians rarely encounter price information in practice, payers' reimbursement policies and formularies developed by Pharmacy and Therapeutics Committees were identified as potential tools for supporting appropriate use. For example, a payer could choose not to reimburse for the use of a narrow-spectrum antibacterial drug in the absence of confirmatory diagnostic tests.

Participants also suggested that utilization of more expensive drugs would be monitored more closely by hospital management, payers, and other key decision makers. Others felt that incorporating additional payments based on quality measures could also help direct therapy. Overall, participants felt that the health care system is undergoing a significant transition towards evidence-based, accountable, and cost-effective practices, and that new antibacterial drugs are likely to be used more judiciously than they would have prior to the transition.

Stewardship Solutions for Commonly Prescribed Antibacterial Drugs

Developing novel antibacterial drugs is necessary for combatting drug-resistant pathogens, but as illustrated above, there are significant challenges to ensuring that antibacterial drugs are used safely and sustainably to protect their efficacy for as long as possible. This applies to novel and existing therapies for treatment of both serious and less serious infections. In the afternoon, workshop participants turned their focus towards overuse of commonly prescribed antibacterial drugs (e.g., for treatment of acute upper respiratory infections). Participants highlighted variable global patterns of antibacterial utilization for common infections, driven in part by the availability of antibacterial drugs without a prescription in many countries. Presenters also indicated that within the U.S. there is regional variation in prescribing rates that present opportunities for targeted interventions.

Historically, antibacterial drugs that treat common conditions have been inexpensive, which has likely contributed to their overuse. Participants felt that inappropriate use has been further accelerated by retail and grocery store pharmacies that provide antibacterial drugs to patients at low prices or even no cost. Participants noted that it is easier for a physician to prescribe an antibacterial drug than to explain why a prescription is unnecessary, and that physicians may feel pressured to prescribe a drug by patients or parents. Some evidence indicates that up to half of all antibacterial drug prescriptions may be inappropriate in some populations,[10] and we still lack a clear understanding of which patient populations are most likely to benefit from antibacterial drug therapy. In addition to low costs, participants agreed that antibacterial drug use has also been driven by a general perception of drug safety, even though the drugs have known adverse effects, some of which may be serious (e.g., *C. difficile* infection).

Efforts to implement stewardship programs have had some success. The Centers for Disease Control and Prevention's (CDC) Get Smart: Know When Antibiotics Work program has sought to tackle misconceptions about the efficacy of antibacterial drugs and to raise awareness about the risks of these products. CDC has also worked with expert clinicians to revise treatment guidelines for some common conditions[11] in order to promote appropriate use. Other participants cited programs that promoted watchful waiting that allow a patient or parent to fill a prescription only if symptoms persist after three days. However, participants felt that generally the impacts of stewardship programs in the ambulatory care setting were modest and often did not have lasting effects. They identified the need for more practical, cost-effective, and sustainable stewardship solutions that can be more readily integrated into current clinical practice and scaled up.

Stakeholders identified improved communication with policymakers, clinicians, and patients about the benefits and risks of antibacterial drug use as a promising approach to achieving stewardship goals. Stakeholders felt that it was important to emphasize that benefits associated with antibacterial drug use are modest at best or unclear for a number of non-serious conditions – including sinusitis, otitis media, and bronchitis – and that there were opportunities to identify patient-reported outcomes and characteristics that correlate with a better response to antibacterial therapy. Participants reported some success in education efforts geared towards parents and children and identified academic detailing or continuing medical education as potential mechanisms for communicating with providers about evidence-based benefit-risk assessments in their everyday practices.

Finally, participants identified the need for monitoring and evaluation of physician prescribing practices and the impacts of stewardship efforts. A number of stakeholders suggested that physician or health plan report cards or quality measures could serve as tools to incorporate the wider health care system and create incentives for good stewardship practices.

Conclusion

Many are optimistic that as the basic science progresses, clinical models that integrate new technologies could support the development and appropriate use of more targeted therapies. For example, innovative sequencing-based diagnostics are increasingly being used to identify infectious pathogens and their susceptibilities soon after patients arrive in an acute care setting. Further diagnostic innovation could usher in an era of pathogen-focused drug development programs and targeted therapies, in much the same way that the use of tumor markers has revolutionized oncology. There was broad consensus among stakeholders that major innovations in diagnostics will be needed to support pathogen-focused drug development and appropriate use of targeted therapies.

Despite the significant economic, scientific, and regulatory challenges that have significantly slowed antibacterial drug development, targeted antibacterial therapies are currently in the pipeline. And newer products may soon enter novel regulatory pathways, such as the Limited Population Antibacterial Drug pathway, a key provision in the Antibiotic Development to Advance Patient Treatment (ADAPT) Act of 2013.[12] Regulatory frameworks and stewardship programs to support these products will need to be thoughtfully designed to encourage further investment and innovation in this space.

To that end, it will be important for drug regulatory agencies to provide clarity regarding the requirements for pathogen-focused drug development. If pathogen-focused drug development occurs via a broad "umbrella" regulatory framework, it will be necessary for sponsors and regulators to have a common vocabulary and expectations for development programs. Participants agreed that development programs and evidentiary requirements should generally be guided by an experimental drug's spectrum of activity, the incidence of the pathogen, and the threat that the pathogen poses to public health. The finalization of guidances will provide some clarity for development programs; however, there will still be a need for drug sponsors to have multiple levels of discussion with

regulators in different countries, given the complexities associated with developing targeted therapies and the fact that companies are developing drugs for the global market.

While there are a number of promising regulatory strategies for strengthening the antibacterial drug pipeline, there is room for economic incentives to lure manufacturers into the antibacterial drug market. Comprehensive reimbursement reforms that recognize the real value of antibacterial drugs in protecting public health and that encourage appropriate use and better health outcomes are ultimately needed. Such reforms could complement innovative regulatory strategies and help move antibacterial drug development efforts forward.

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