Facilitating Antibacterial Drug Development

As the prevalence of drug-resistant bacteria continues to rise, there is a pressing need for new drugs to combat infections by these organisms. However, research and development in this area has slowed, with only a few large pharmaceutical companies supporting active antibacterial drug discovery programs. With only two new classes of antibiotics having been introduced to the market within the past 30 years, the increase in the number of antibacterial drug resistant infections creates a pressing public health concern. While there have been recent initiatives by U.S. policy-makers to spur the antibacterial drug development pipeline that seek to increase market exclusivity, streamline the regulatory process, and provide opportunities for smaller, more rapid, and less expensive clinical trials for qualifying products,[1] more attention needs to be paid to innovating the antibacterial drug development paradigm.

Workshop Scope and Objectives

While challenges to antibacterial drug development may be scientific, methodological, regulatory, or economic in nature, this workshop will focus on exploring solutions to methodological and regulatory challenges that can make the drug development process more efficient, including 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.

Compared with some other therapeutic areas, conducting clinical trials to assess the efficacy and safety of new antibacterial drugs poses significant challenges. An initial step toward developing best practices for antibacterial clinical trial design is gaining a better understanding of and advancing the science in clinical trial design for bacterial infections. Some of methodological challenges that may need to be addressed for conducting antibacterial clinical trials include the following:

- Design of trials
    - The role of non-inferiority (NI) trials – Recent questions have focused on scientific issues related to non-inferiority trials and the evidence being relied on to design NI trials and choose NI margins. While NI trials have traditionally been used to assess the efficacy and

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[1] The Generating Antibiotics Incentives Now (GAIN) Act introduced by US Senate and House of Representatives seeks to increase the market exclusivity for qualifying antibacterial products by an additional five years and to qualify these products for priority review and fast-track approval by the U.S. Food and Drug Administration (FDA). Another effort is the Infectious Diseases Society of America's proposal for a new FDA approval mechanism known as "Limited Population Antibacterial Drug" (LPAD). This mechanism, limited to potential treatments for serious infections with few or no therapeutic options, allows for smaller, more rapid, and less expensive clinical trials. Drugs approved through this mechanism would be restricted to a narrow indication to encourage prudent use, which could help to combat overuse of the drug and resistance.

safety of new antibacterial drugs, perhaps other trial designs may be feasible in certain instances.

- o Further endpoint development – There are a number of ways to assess the efficacy of an antibacterial drug: the drug's ability to kill the microorganism, reduction in mortality, or reduction in patient symptoms. The variety of available endpoints when assessing a drug's performance may create a need for the development of a set of commonly agreed upon endpoints that are reliable, well-defined and clinically relevant to allow the medical community to assess and compare product performance.[2] This may require gaining a deeper characterization of currently used endpoints or developing new endpoints. It may also be valuable to incorporate patient-reported outcomes among antibacterial trial endpoints. Additionally, developing early endpoints that are good predictors of outcomes has the potential to expedite the clinical trials process. However, long-term outcomes will certainly remain of interest to patients, providers, regulatory authorities, payers, and a range of other stakeholders.
- o Use of Bayesian methods: Unlike a frequentist approach, Bayesian methods take advantage of prior knowledge from a variety of sources. Bayesian methods can potentially play an important role in the design of clinical trials. However, it is important to carefully consider appropriate sources of prior knowledge and how to use this information. If appropriately applied, Bayesian methods have the potential to reduce the population required for the trial through adaptive trial designs.[3] A number of other therapeutic areas have successfully applied Bayesian methods to clinical trial designs, and Bayesian methods may be a useful tool for antibacterial drug clinical trials.
- Implementation of trial delivery
  - o Enrolling correctly diagnosed patients – Limitations of currently available diagnostic tests may lead to enrolling patients that do not have the required condition for the trial or not identifying patients who have the condition. Improved diagnostics could reduce the required sample size and, hence, the cost of and time required to conduct the clinical trial.
  - o Need for immediate and acute treatment – Infectious diseases usually require urgent initiation of antibacterial drug therapy. Because of this, patients may have already received an early dose of antibacterial therapy by the time they are enrolled in a clinical trial. The effects of early doses of antibacterial therapy can introduce uncertainty when evaluating the effect of a new drug and is a particular concern for NI trials.
- Interpretation and analysis of results
  - o Inclusion of other sources of information about a drug's performance – The evaluation of a product's efficacy and safety can account for other sources of information to complement data obtained from clinical trials. This may include historical data, data from animal models, data pooled from infection sites across multiple body sites, and pharmacokinetics and pharmacodynamics information.

The list above does not represent an exhaustive list of methodological and regulatory challenges relevant to antibacterial drug development. During the meeting, participants are encouraged to consider innovative approaches to address these and other methodological and regulatory challenges that are most pressing to facilitate the development of new antibacterial drugs.

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[2] FNIH Biomarkers Consortium Project: http://www.fnih.org/press/blog/biomarkers-consortium-project-aims-develop-well-defined-endpoints-antibacterial-clinical.
[3] Donnan GA and Davis SM. "Is the Bayesian Approach Ready for Prime Time? Yes!" *Stroke*. 2005; 36:1621-1622.

Workshop Overview

Panel 1: Existing Paradigms for Antibacterial Drug Development

The first panel of the workshop is intended to explore the current landscape for antibacterial drug development, with particular attention to unmet clinical needs, characteristics that set the infectious disease clinical setting apart from other therapeutic areas, important aspects of the current drug development paradigm, and the role of regulatory science. Potential questions for discussion during this panel may include the following:

- What characteristics of the infectious disease clinical setting (e.g., distinct biologic characteristics of acute infections, clinical use of antibacterial drugs, diversity of patient profiles/disease severity, antibacterial resistance) set antibacterial drug development apart from development of other medical products?
- What are the most pressing unmet clinical needs that new antibacterial drugs could address?
- How has the current drug development paradigm affected the development of new antibacterial drugs?
  - What is the role of non-inferiority trials in antibacterial drug development and what challenges are associated with this design (e.g., identification of appropriate patient populations, use of diagnostics, endpoints, non-inferiority margins)?
  - Do other sources of information about antibacterial drug performance (e.g., historical data, animal models) currently inform trial design in an effective way?
  - What are the feasibility challenges impeding trial delivery (e.g., urgent initiation of treatment, ethical issues of non-treatment)? Could rapid diagnostics, if available, help address these challenges?
- How does regulatory science influence antibacterial drug development?
  - What is the minimum evidentiary standard required to demonstrate safety and efficacy?
  - What is the current state of regulatory science (e.g., risk-benefit evaluations based upon severity of infection and therapeutic alternatives, choice of appropriate endpoints to evaluate efficacy, evidentiary requirements for approval) for review of antibacterial drugs?
- What activities are currently being conducted to support antibacterial drug development?

Panel 2: Pharmacokinetics and Pharmacodynamics (PK/PD) in Antibacterial Drug Development and Bayesian Methods in Clinical Research

This panel will explore the potential role of pharmacokinetics and pharmacodynamics and Bayesian methods in the antibacterial drug development program, including how these tools can be appropriately applied and the strengths and limitations of their use. Potential discussion questions may include the following:

- What is the role of PK/PD in drug development?
  - What can be learned from animal models?
  - What is the role of PK/PD from clinical trials in evaluating drug effect?
- How can Bayesian methods be applied to antibacterial drug development?
  - "Bayesian 101:" What is it? How does it work? How is prior Bayesian evidence developed?
  - How have Bayesian methods been applied in other fields?
  - How can Bayesian methods be applied to assess efficacy of new antibacterial drugs?
  - What are the strengths and limitations of applying Bayesian approaches in assessing antibacterial drug efficacy?
  - What are appropriate statistical approaches to smaller clinical trials?

Panel 3: Novel Approaches to Further Antibacterial Drug Development: New Approaches to the Clinical Development Program

This panel will explore new methods and tools to improve the development of antibacterial drugs, including new approaches to research, analysis, and evaluation of evidence. Potential discussion questions may include the following:

- What new research approaches could be applied to expedite development of new antibacterial drugs? Potential research approaches may include the following:
    - Use of innovative clinical trial designs from other therapeutic areas;
    - Use of alternate/new sources of data to characterize safety and efficacy (e.g., use of historic data, existing databases); and
    - Use and development of alternate clinical endpoints.
- Are there new regulatory approaches that could facilitate evaluation and access to new antibacterial drugs and provide an understanding of their benefits and risks?
- How can these new research and analysis tools bridge gaps in the existing antibacterial drug development paradigm? What are strengths and limitations of these new tools?
- Are there approaches that can take advantage of the totality of evidence in assessing safety and efficacy of new antibacterial drugs? What data elements could contribute to this assessment? What or how can these elements contribute to the evidence?

Panel 4: Outlining the Path Forward

The last panel of the day will outline practical next steps for advancing antibacterial drug development and consider the role of different stakeholder groups to advance the proposed next steps. Potential discussion questions may include the following:

- What are the short- and long-term next steps for advancing the antibacterial drug development enterprise? What will be the role of different stakeholders in advancing these steps?
- How could clinical trial consortia or pre-competitive collaboration among stakeholders contribute to antibacterial drug development efforts?
- What advances in regulatory science will be necessary to facilitate the next generation of antibacterial drug development?
- What is the role and potential impact of rapid diagnostic tests on drug development? What is a realistic timeframe for availability of these tests?
- What is scientifically and practically achievable, given the types of evidence that can realistically be generated during antibacterial drug development? How might evaluations of risk and benefit be re-calibrated to allow appropriate decision making based on imperfect information?

This meeting is intended to be highly interactive, and all participants are encouraged to consider novel solutions, some of which may come from lessons learned in other therapeutic areas, that will address this critical public health problem. This meeting will be a success if, by the end of the meeting, participants can develop a list of practical next steps for advancing the antibacterial drug development enterprise and outline roles and responsibilities for advancing these steps.