Antibacterial Drug Development:
Issues in the Design of Trials in Patients with Unmet Needs and in Patients with Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia

Executive Summary of Meeting held October 11-12, 2012

Sheraton Crystal City Hotel, Arlington, Virginia

Clinical Trials Transformation Initiative (CTTI)

Meeting background

Research and development of new antibacterial drugs has slowed but the prevalence of antibacterial resistance continues to rise, creating an urgent unmet public health concern. This two-day workshop, organized and facilitated by the Clinical Trials Transformation Initiative (CTTI)[1], convened a diverse group of stakeholders representing hospitals, academia, the pharmaceutical industry, government agencies, and patient advocates to understand the challenges in addressing the need for new antibacterial drugs and to explore potential solutions for meeting this need.

The goal of the first day of the workshop was to define potential pathways and explore new paradigms to accelerate the development of new antibacterial drugs that would address unmet medical need, including discussing acceptable levels of uncertainty related to the risks and benefits of such treatments. The second day focused on issues in clinical trial design including endpoints and operational efficiencies specific to the development of antibacterial drugs for treating patients with hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP).

A general summary of the meeting is provided below. The agenda, presentations and participant list are available [2]

Day 1: Exploring a new paradigm for antibacterial drug development in areas of unmet need

Presentations in Sessions 1 and 2 described the current unmet need for antibacterial drugs and the epidemiological landscape of bacterial resistance patterns, as well as general examples of types of data available from smaller development programs. A moderated discussion that followed considered the possibilities and limitations of small development programs for a targeted population to address areas with an unmet need.

Participants expressed that it is critical for all stakeholders to work together, particularly with regard to characterizing novel research models and seeking alternatives to traditional superiority trials.

1. Targeted smaller development programs

The difficulty of enrolling trials with patients with an unmet need, which tend to be typically limited in size and heterogeneity was discussed (e.g., patients with rare infections or with emerging resistance), along with strategies to enhance enrollment, and possible solutions were explored. Specific suggestions included: performing studies in geographic areas where the pathogen is endemic, or where there is a greater likelihood of encountering serious infections; improving rapid diagnostics; and creating large networks of research sites to ensure consistency and efficiency in the execution of innovative trials. The latter may also facilitate collaboration and improve coordination for a more rapid response to newly identified outbreaks of resistant pathogens.

The discussion included:

- The use of primary endpoints that have not been typically used in the past to support approval (e.g., those that reflect improvement in patient outcomes, including survival)
- The use of pharmacokinetic/pharmacodynamic (PK/PD) to support dose selection, the exposure–response relationship, and whether it may have the potential to be reasonably likely to predict clinical benefit.
- The need for accepting greater uncertainty in trial designs and approval/registration packages since attempts to reduce uncertainty may greatly delay development for little gain. The labeling of drugs approved in this manner should reflect the available knowledge and allow clinicians to exercise their best judgment about the known benefits and acceptable risks.
- A consideration should be given to reimbursement and business models to accommodate these novel approaches to address economic issues impacting antibacterial research and development.

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[1] https://www.ctti-clinicaltrials.org/

[2] https://www.ctti-clinicaltrials.org/anti-bacterial-drug-development-issues-in-the-design-of-trials-in-patients-with-unmet-need-and-in-patients-with-hospital-acquired-and-ventilator-associated-bacterial-pneumonia/

2. Innovative approaches to clinical trial design and data analyses

Session 3 began with presentations that proposed novel approaches to clinical trial design and data analyses in antibacterial drug development programs intended for patients with unmet need.
The moderated discussion that followed included

- A focus on the challenges of using traditional superiority trials in patients with severe infections and the feasibility of the novel approaches was presented in this session. A path forward could include a development/approval pathway using a smaller clinical trial database, perhaps similar to the approaches currently used for rare diseases. The limitations and uncertainty of such a development program should be clearly conveyed through education, for example, of patient advocacy groups, advisory committee members, scientific and academic research communities, private-practice clinicians, and other constituencies.
- Well-defined and reliable efficacy endpoints should be used in trials enrolling patients with unmet need. There were some concerns expressed with the use of all-cause mortality as an efficacy endpoint in the programs under discussion because of factors including the introduction of "noise" into the analysis and a potentially higher burden of proof given the multi-factorial nature of mortality in seriously ill patients.
- The need to identify suitable control groups for various study design scenarios such as best available therapy, concurrent susceptible/resistant populations, and historical cases, and the possibility of cluster randomization were also explored.

3. Identifying potential solutions to development of drugs for unmet need

In Session 4, a presentation on the patient perspective on antibiotics and clinical research was followed by a panel moderated discussion. Numerous approaches to innovative solutions mentioned in previous sessions that could be considered by the clinical research enterprise were discussed at greater length:

- The option for accelerated approval, based on a surrogate endpoint reasonably likely to predict clinical benefit followed by a post-approval confirmatory trial, was considered worthy of further exploration as a possible approach for addressing unmet needs. Such approvals, based on smaller development programs, could be strengthened to include antibiotic stewardship programs that could assist practitioners in promoting appropriate use.
- Postmarketing surveillance, with tools such as the Agency's Sentinel Initiative could be considered. Proposals for new regulatory approval mechanisms, such as the Limited Population Antibacterial Drug[3] approval mechanism, were mentioned as a potential approach for addressing the unmet need for new antibacterial drugs.
- The need for the clinical research enterprise to embrace and participate in establishing a new model and to foster collaboration among stakeholders, including the development of clinical networks, was reiterated.
- The existing regulatory mechanism of accelerated approval was discussed, although a surrogate endpoint reasonably likely to predict clinical benefit was not clearly identified.

The group acknowledged that although randomized clinical trials (RCTs) are the gold standard for demonstrating efficacy, in this era of antibiotic resistance there is a critical unmet need for new antibacterial treatments necessitating the use of alternative research models. Therefore, additional work must be done on acceptable study designs, definitions, data sources, regulatory/operational infrastructure, diagnostic capabilities, and changing the research ecosystem in order to facilitate antibacterial drug development.

Day 2: Issues in Clinical Trial Design for Drug Development to Treat Patients with Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HABP/VABP)

Sessions 1 and 2 reviewed the current approach to clinical programs and efforts to address unmet need in HABP/VABP, including an overview of clinical endpoints, biomarkers, clinician-reported outcome measures, and surrogate endpoints that are currently used or could be used in HABP/VABP clinical trials.

[3] http://www.idsociety.org/2012_LPAD_Proposal_Backing/

4. Endpoints in HABP/VABP trials

Discussion that followed the presentations addressed:

- Feasibility of clinical endpoints, biomarkers, and other surrogates in HABP/VABP studies**.** The advantages and challenges of using all-cause mortality as an efficacy endpoint were specifically discussed. Mortality has some advantages as an endpoint for HABP/VABP studies; it is a direct measure of clinical benefit (i.e., how a patient feels, functions, or survives), and data collection is relatively simple. However, mortality in patients with HABP/VABP may be affected by many other factors that may not be directly related to the exposure and/or the mechanism of action of the study drug, such as use of rescue therapy and withdrawal of patients from the study. Mortality captured as an endpoint earlier in therapy was discussed (e.g., at day 3 to day 5). However, based on estimates of potential sample sizes using an odds ratio metric[4,] the use of mortality as an early endpoint would reduce event rates and necessitate increased sample sizes. While mortality is an important, readily available outcome, there might be other suitable efficacy endpoints, mortality is still important for safety and sensitivity analyses.

  Alternatives to mortality endpoints were discussed and the group was unable to identify a standardized, reliable non-mortality endpoint currently used in HABP/VABP trials. Several endpoints for treatment effect and as potential early surrogates for mortality were suggested. These included:

Composite symptoms, including time to resolution	Change in bacterial load as in HIV/ HCV
Duration of ICU/or hospital stay	Need for rescue antibacterial treatment
Time on ventilator	Change in oxygenation measures

  Concerns related to these endpoints were also raised, including variability among patients and sites calling for increased sample size, unknown sensitivity and specificity, and a higher likelihood of missing data in some cases (which could be mitigated by an endpoint early in therapy). Additionally, the lack of historical or recent data on these variables would make the determination of NI margins difficult. The merit of a composite endpoint including mortality, (i.e. death plus other non-fatal events) that herald a patient's lack of response to antibacterial drug therapy, was discussed.

- Collaborative efforts for data sharing and mining across available clinical databases from different organizations and the clinical research enterprise could accelerate the identification, development, and validation of potential endpoints that are alternatives to mortality. A similar recommendation to streamline development of such outcome measures through pooling and analyses of datasets across organizations was made in a recent report [5] from the President's Council of Advisors on Science and Technology (PCAST). The Biomarkers Consortium, FNIH,[6] was considered by the group to have an opportunity play a key role in this effort, as they have in other similar efforts related to efficacy endpoints in CAP.

- The need for education and setting appropriate expectations for acceptance of both accelerated approval and the use of alternative endpoints in antibacterial drug development. Publishing the results and devoting sufficient resources to efforts within industry, academia, patient organizations, and government agencies will be critical in this regard. Some participants maintained that development of these drugs is currently being held to an unreasonably high standard relative to other therapeutics, They further expressed the need for regulators, clinicians, payers, and the public to recognize that in order to expeditiously develop new drugs to treat serious infections, smaller clinical development programs with inherent uncertainties may be necessary and this will need to be considered in benefit-risk discussions.

Identifying potential solutions to HABP/VABP

Session 3 began with a presentation that focused on current practices and potential strategies to improve the operational efficiency and feasibility of HABP/VABP studies.

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[4] http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm242307.htm

[5] http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf

[6] http://www.biomarkersconsortium.org/

The moderated discussion included:

- How design and operation of clinical trials for HABP/VABP could be streamlined to be faster and more cost effective. Several ideas were proposed, including use of electronic medical records (EMR) to prescreen for enrollment into trials, and also to streamline data collection, sharing, and analyses. The group discussed how the burden of data collection can be reduced for most trials and sites by using broad inclusion/exclusion criteria and collecting only essential data. EMRs should be used whenever possible to generate screening criteria, historical/concurrent controls, estimated safety and efficacy event rates, etc.
- The use of more realistic, plain-language consent forms, preapproval of sites for enrollment in future studies and having a subset of sites collect supplemental data would also simplify data collection.
- The recent FDA guidance on collection of safety data[7] should be promoted within and outside the agency, so that all stakeholders become familiar with the FDA's current thinking on this topic, so as to prevent "defensive data collection." The group acknowledged that differing standards for data collection outside the United States remains a major issue; the regulatory agency with the most extensive requirements will control data collection for the rest of the world.
- Perception of risk from medications in general, and antibiotics in particular, may be unrealistic. The concept of acceptable risk and the role of government in assessing risk must be communicated to the public to set clear expectations and forestall misunderstandings.
- To accelerate antibacterial drug development, future activities could be modeled after organized research groups, such as the AIDS Clinical Trials Group (ACTG) network[8], whose efforts resulted in the approval of AZT 2.5 years after the first antiviral activity against HIV had been detected *in vitro*.

The meeting was adjourned after discussing possible next steps for the group to pursue:
In the short term: participants could plan how best to pool datasets and query them for factors related to drug response (which could then be studied as alternative endpoints to mortality), in addition to considering anticipatory consent models and standardization of processes.

In the long term: EMR mining could be expanded to build prospective datasets for validation against current trials. Companies might think about collaborating on 3-arm trials, which would eliminate competition for sites and reduce development time. Collaboration in general will be critical to address this unmet medical need.

[7] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291158.pdf
[8] https://actgnetwork.org/