A Collaborative Model for Endpoint Development for Acute Bacterial Skin and Skin Structure Infections and Community-Acquired Bacterial Pneumonia

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(See the Reviews of Anti-Infective Agents Invited Article by Talbot et al, on pages 1114–21.)

Two important diseases in need of new antibacterial drugs are acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP). These are common infections in the United States, with millions of patients treated annually. The identification of well-defined and reliable efficacy outcome measures for ABSSSI and CABP would greatly assist in clinical trials of new antibacterial drugs to treat the 2 diseases. With a clear clinical and regulatory need for outcome measures for ABSSSI and CABP, we approached the Biomarkers Consortium of the Foundation for the National Institutes of Health about assembling a project team. In this issue of Clinical Infectious Diseases, the project team of the Biomarkers Consortium of the Foundation for the National Institutes of Health (FNIH PT), as part of their ongoing work, provides a summary of data reviews, opinions, and recommendations for primary efficacy outcome measures for ABSSSI and CABP that will support development of new antibacterial drugs [1]. Additional work is planned to further improve and refine outcome measures.

The FNIH PT brought together a wide range of experts in infectious diseases, statistical sciences, and clinical trials research from the academic research community, biopharmaceutical companies, and government. A unique perspective of the FNIH PT was the retrospective evaluation of outcome measures in data from various clinical trials of biopharmaceutical sponsors. The enormous research value in evaluating these data within a single collaborative project is reflected in the work of the FNIH PT and its presentation in this issue of Clinical Infectious Diseases. An especially important contribution of the data evaluation by the FNIH PT is the public access that it provides in the form of documents submitted in response to each of the Food and Drug Administration draft guidance documents for ABSSSI and CABP [2, 3].

The review of the historical literature, summarized by the FNIH PT, describes the past performance of antibacterial drugs in the context of an earlier endpoint that demonstrates treatment benefit in ABSSSI and CABP. These findings are important because noninferiority clinical trial designs require that pertinent clinical data determine the past performance of an active control [4]. Clinical development programs for ABSSSI and CABP use active-control noninferiority trial designs.

The outcome measures recommended by the FNIH PT provide a scientifically and clinically sound means for evaluating efficacy for new drugs in the treatment of ABSSSI and CABP. For example, an outcome measure for CABP based on improvement from the patient’s perspective, relatively early in therapy (eg, day 3 to day 5), is given in the FNIH PT retrospective analysis. An outcome measure for ABSSSI based on the control of lesion spread, also relatively early in therapy (eg, a ≥20% decrease in lesion area at day 2 to day 3 vs baseline), is similarly described through the group’s scientific and clinical evaluations. Demonstrating noninferiority on the basis of these outcome measures establishes clinical benefit for trials of new antibacterial drugs for treatment of these illnesses.

Clinical development programs incorporating these outcome measures right now should be reassured that we will accept efficacy endpoints based on improvement in symptoms for CABP and control of lesion spread for ABSSSI, even as further work is being done by the FNIH PT on its next phase of the project. Our recent review and approval of the...
new drug ceftaroline fosamil incorporated similar efficacy outcome measures as recommended by the FNIH PT.

Early outcome measures, as supported in the work of the FNIH PT, have occasionally been criticized in favor of efficacy measurements determined at the completion of therapy or beyond. Later outcome assessments are always important to evaluate. Clinical cure at the completion of therapy or beyond should be assessed in clinical trials [5]. However, the work done to date has not established the past performance of antibacterial drugs on a clinical cure endpoint at the completion of therapy or beyond.

Nevertheless, any clinical trial for ABSSSI or CABP should incorporate both early as well as late outcome assessments. Such an approach should also enable the use of the trial for multiple regulatory authorities.

With the identification of outcome measures for use in the development of ABSSSI and CABP treatments, FNIH PT has turned its attention to the next phase in the further development of outcome measures and to address remaining gaps in measurement. The goal of this next phase is to refine and further develop reliable and well-defined assessments suitable for use in clinical trials and available to all interested parties. This project has been launched, and a formal request for proposals has been issued to complete a qualitative research phase of outcome measures development, involving both literature searches and patient interviews.

We are grateful to the FNIH PT for the time and effort they have invested in defining better outcome measures for ABSSSI and CABP. This work has already had a favorable impact on the field of antibacterial drug development in these diseases. These outcome measures and the identification of further refined outcome measures based on the planned additional work of the FNIH PT will facilitate clinical development of new antibacterial drugs.

Notes

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Disclaimer. The opinions in this report are those of the authors and do not necessarily represent the views of the US Food and Drug Administration. The authors are regarded as nonvoting members of the FNIH project team. Available at: http://www.regulations.gov/#!docketDetail; dct=FR%252BPR%252BN%252BO%252BSR%252BSR; rpp=25;po=0;D=FDA-2010-D-0433. Accessed 26 June 2012.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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