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Executive Summary: Workshop on Issues in the Design and Conduct of Clinical Trials of Antibacterial Drugs in the Treatment of Community-Acquired Pneumonia

Brad Spellberg[1], **Thomas R. Fleming**[2], and **David N. Gilbert**[3]

[1]*Division of Infectious Diseases at Harbor–University of California at Los Angeles (UCLA) Medical Center, Torrance, and the Geffen School of Medicine at UCLA, Los Angeles* [2]*Department of Biostatistics, University of Washington, Seattle* [3]*Providence Portland Medical Center and Oregon Health Sciences University, Portland*

For several years, the Infectious Diseases Society of America (IDSA) and its Antimicrobial Availability Task Force (AATF) have worked to reverse the decline in development of new antibacterial agents in the United States and throughout the world [1–4]. Economic cost-benefit considerations are one factor influencing new antibiotic development. Another is uncertainty about the proper design and conduct of clinical trials of antimicrobials so as to reliably evaluate drug safety and efficacy [1].

The IDSA has encouraged the availability of guidance documents from the US Food and Drug Administration (FDA) so as to clarify clinical trial designs for specific infectious diseases indications. There is a need for a reevaluation of clinical trial guidance for community-acquired pneumonia (CAP). CAP is a major cause of morbidity and mortality [5–7]. In addition, the emergence of drug-resistant pathogens and increased virulence of drug-sensitive bacteria are incentives to encourage discovery and development of effective drugs to treat CAP.

The purpose of the CAP Clinical Trial Workshop, held on 17 and 18 January 2008 and cosponsored by the FDA and IDSA, was to discuss in depth evolving scientific information relevant to the design and conduct of CAP clinical trials. Two formal goals were stated. The first goal was to examine critical issues in the design and conduct of clinical trials of antibacterial drugs in the treatment of CAP, to include use of molecular methods to establish an etiologic diagnosis and the implications of emerging scientific tools that assist in the diagnosis of the etiology of CAP. The second goal was to discuss clinical end points and relevant statistical issues. Major discussion focused on the design of clinical trials, including whether placebo (or no-treatment) controls or active controls were appropriate; if active controls are used, whether trials should have a superiority or a noninferiority design; and if a noninferiority trial is appropriate, an evidenced-based method that can be used for determination of an appropriate noninferiority margin.

Although most recent clinical trials for CAP have used noninferiority designs, reevaluation of the appropriateness of such a design has been influenced by insights from extensive methodological research in this area as well as growing experience with their use in clinical

Reprints or correspondence: Dr. David N. Gilbert, Providence Portland Medical Center, 5050 NE Hoyt, Ste. 540, Portland, OR 97213 (E-mail: D.Gilbert@providence.org).

research [8]. The International Congress on Harmonization (ICH) guidances E9 and E10 [9, 10] indicate that noninferiority trials are appropriate only when all of the following are true:

1. Historical study data document a clear treatment effect of a standard comparator drug. The data provide a reliable, reproducible, and precise estimate of effect on a specific efficacy end point in a specific patient population. This treatment effect is the margin of efficacy of the standard comparator above placebo/no treatment (so-called "M1").
2. The standard comparator drug is expected to have an efficacy in the current trial that is similar to that documented previously.
3. The margin of inferiority (so-called "M2") to be used in the trial of the new/experimental drug must preserve much of the treatment effect of the active comparator drug on the same end point (i.e., M2 < M1) and should exclude clinically meaningful differences.

The ICH guidances present several scientific challenges if noninferiority trial designs are used for the evaluation of treatments of CAP. First, antibiotics became available for the treatment of CAP in an era prior to the use of rigorous, randomized superiority trials. Further, patient populations and clinical end points were less carefully defined in older clinical research, compared with research in the modern era. However, in the early days of antibiotic use, there was greater emphasis on making a microbiological diagnosis. Compared with the initial use of sulfonamides and penicillin, modern trials may differ in patient selection, level of supportive care, details of treatment regimens, and the definition and evaluation of study end points.

The workshop was broken into 2 separate sessions on consecutive days, the first dealing with "mild-to-moderate" CAP and the second focusing on "severe" CAP. Typical patient scenarios were presented so as to focus the discussion. "Severe" refers to baseline variables that predict worse outcomes independently of the intervention administered. This separation of topic by disease severity focused the discussion on issues relevant to oral therapy (mild-to-moderate CAP) or intravenous therapy (severe CAP) in clinical trials. For patients in both settings, speakers discussed key elements of clinical trial design, including safety issues, selection of patients for enrollment, diagnostic tools to establish microbiological etiology, definition of appropriate clinical end points, selection of an appropriate comparator agent, and whether to use a superiority or a noninferiority trial design. Additional discussion focused on the appropriate justification of noninferiority margins. This supplement contains summaries of the presentations given at the symposium by thought leaders on each of these topics.

Specifically, Drs. Powers, Fleming, Higgins, and Temple reviewed the scientific requirements that underpin the justification, design, execution, and analysis of noninferiority trials. Dr. Murphy discussed the feasibility of use of a placebo control for clinical trials for CAP, and Drs. Echols and Tillotson provided opinions about the feasibility of completion of superiority or noninferiority trials from the perspective of industry. Drs. Gilbert, Powers, File, Higgins, Echols, and Musher identified and evaluated potential clinical end points for CAP trials.

Drs. Nolte, Niederman, and Klugman reviewed the state of the art in molecular diagnostics and biomarkers with the potential to enrich patients enrolled for subjects with a bacterial etiology of their CAP, as opposed to a viral etiology. This enrichment for patients infected by susceptible bacteria is particularly important to minimize diluting estimates of treatment effect. Such dilution reduces the statistical power of superiority trials and tends to bias noninferiority trials toward committing a false-positive error. Drs. Psaty, Talbot, Oussova, and Boucher provided insight into safety issues specific to CAP clinical trials and identified complexities in blinding treatment regimens. Drs. Fine and Mandell discussed identification and stratification of patient populations enrolled in the 2 trial scenarios. Classification of patients by the severity of their pneumonia was emphasized.

Dr. Bratzler discussed the potential use of the national Medicare databases to guide the design of trials, and Dr. Bartlett critically evaluated the need, or lack of need, for combination therapy for CAP. Dr. Ambrose discussed the potential for pharmacokinetic/pharmacodynamic parameters to both design rational treatment regimens and predict regimens with a low likelihood of therapeutic benefit. Finally, Dr. Singer provided an overview of the historical data regarding the outcomes of CAP in the preantibiotic and immediate postantibiotic era. The historical data are of particular import in the determination and justification of appropriate margins for noninferiority trials.

In summary, the workshop presentations provide a sound platform that can serve as the basis for contemporary FDA guidance to industry on acceptable design and conduct of future clinical trials of new antibacterials for patients with CAP.

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