Antibiotic development has decreased significantly, in part because of recent changes in regulatory requirements in the United States. These changes both decrease the probability of technical and regulatory success for a new antibiotic for which marketing approval is sought and motivate the pharmaceutical industry to focus its research efforts on other therapeutic areas. There is a growing, unmet clinical need for new antibiotics, because of bacterial resistance to approved drugs; however, there are few candidates in development, especially new oral agents for treatment of community-acquired respiratory infections. The answers to important questions about the benefit of antibacterial treatment for community-acquired pneumonia and the publication of clear guidance for future clinical studies will support future investments. We discuss the underlying issues and offer some alternative strategies to enable improvements in clinical trial design for community-acquired pneumonia.

The process of the development of antibiotics is based on established methods that include assessment of in vitro and in vivo antibacterial activity, determination of pharmacological characteristics, and, most importantly, performance of randomized, comparative clinical trials. There have been >200 antibiotics approved for clinical use in the past 50 years. Almost all approvals were based on clinical judgment and current statistical reasoning. Antibiotics have been the powerhouse of much of the pharmaceutical industry for the past 50 years, with several antibiotics achieving “blockbuster” status—for example, ciprofloxacin, co-amoxicillin–clavulanic acid, clarithromycin, ceftriaxone, azithromycin, and, most recently, levofloxacin achieved revenues of >$1 billion annually. Currently, only levofloxacin is ranked in the top 20 pharmaceutical products. Despite this past success, and in part because of it, the number of new antimicrobial drug submissions and subsequent approvals has diminished markedly during the past decade. Competition from generics is one reason for the decreasing attractiveness of the antibiotic market. Concomitantly, the continuing development of bacterial resistance to existing products is severely limiting the therapeutic options for patients. This issue has been thoroughly reviewed by Spellberg et al. and other members of the Infectious Diseases Society of America Antibiotic Availability Task Force [1, 2]. The reluctance of large pharmaceutical companies to invest in antibacterials is partially offset by the development of antibacterials by new, smaller biopharmaceutical companies.

THE SHIFTING REGULATORY CLIMATE

Recent changes in the regulatory environment, especially in the United States, have increased the risks associated with the development of new antibiotics. A spate of US Food and Drug Administration (FDA) non-approvals for drugs, such as levofloxacin (750-mg dose) and single-dose azithromycin for acute exacerbations of chronic bronchitis and gemifloxacin for acute bacterial sinusitis [3], were based on the unacceptability of noninferiority trials for these indications. Subsequently, in late 2006, the same 2 indications were removed from the label of telithromycin, because the potential drug benefit (determined on the basis of pre-
vously acceptable noninferiority trials) was no longer considered an adequate demonstration of efficacy when weighed against the risk of adverse events [4]. The FDA's recent guidances regarding noninferiority studies to support the approval of antibacterial drugs [5] and specific study designs for acute bacterial sinusitis [6] emphasize a preference for superiority studies. To date, this approach has not been adopted by non-US regulatory bodies. This lack of consensus among regulatory agencies reverses 2 decades of effort to harmonize international development of antibacterial drugs.

There are several reasons for the reduction in pharmaceutical investment in antibacterial development, but uncertainty about regulatory requirements is the most acute. Although superiority clinical trials for non–life-threatening infections, such as acute bacterial sinusitis, acute exacerbations of chronic bronchitis, and acute otitis media, may be feasible, clinical trials with a superiority design are problematic for more-serious infections, such as community-acquired pneumonia (CAP). There is recent experience in conducting placebo-controlled trials of faropenem medoxomil for acute exacerbations of chronic bronchitis and moxifloxacin for acute bacterial sinusitis [7, 8]. A significant number of ethics committees, institutional review boards, and health authorities have rejected the studies because of the placebo arm. In their view, the safety of the patient is jeopardized (even with close monitoring and “rescue” therapy), and the use of placebo contradicts local treatment standards. The sponsors of these 2 ongoing trials have experienced exceptionally slow enrollment, extending the trial period by several years. In our opinion, it is not feasible to use a placebo or an ineffective drug in a multicenter clinical study of CAP, even for mild CAP.

THE CHANGING UNMET CLINICAL NEEDS

The majority of antibacterial prescriptions for treatment of respiratory tract infections are for generic drugs. Although this trend is likely to continue, the emergence of antimicrobial-resistant bacterial pathogens is a cause for concern. Recent susceptibility data for respiratory pathogens in the 2005–2006 season in the United States show continued high rates of resistance among Streptococcus pneumoniae and Haemophilus influenzae strains. In vitro rates of resistance among S. pneumoniae strains were 62.1% for penicillin and 65.5% for azithromycin, and rates of β-lactamase production among H. influenzae and Moraxella catarrhalis strains were 27.4% and 91.6%, respectively [9]. Levofloxacin demonstrated >99% activity against all 3 respiratory pathogens. However, there is evidence of the emergence of levofloxacin resistance among strains of S. pneumoniae [10]. Selective pressure for more fluoroquinolone resistance is increased by an overreliance on fluoroquinolone empirical therapy, which partly occurs because of the lack of suitable alternatives.

The convergence of drug resistance and the lack of therapeutic options is illustrated by a series of pneumococcal acute otitis media infections caused by multidrug-resistant isolates of a serotype not covered by the licensed protein conjugate pneumococcal vaccine [11]. Serotype 19A has become the predominant serotype causing invasive pneumococcal disease in the United States [12, 13] and elsewhere [14]. Serotype 19A strains are often resistant to β-lactams, macrolides, tetracyclines, and other agents. Only the respiratory fluoroquinolones and some experimental agents are consistently active against these strains [11, 12]. The prospect of needing to resort to fluoroquinolones for treatment of pediatric infections is a great concern, for both resistance and possible safety reasons.

WHAT IS AT STAKE?

Although there is a clear medical need for alternative therapies for respiratory tract infections, regulatory approvals of new drugs will not be successful if they are predicated on the demonstration of clinical superiority for a subset of resistant pathogens. Large, randomized, prospective clinical trials for common infections in which treatment is initiated empirically are required. CAP is the cornerstone of the respiratory tract indications. Demonstration of safety and efficacy in CAP is considered by the FDA to be the anchor for other respiratory tract indications. Now that the FDA is reassessing the clinical trial guidelines for CAP, there is considerable anxiety among pharmaceutical sponsors regarding both the feasibility and the risks (the probability of a negative result) of future clinical drug development trials for CAP. The objectives of this workshop, cosponsored by the Infectious Diseases Society of America and the FDA, were to discuss the issues of clinical trial design for CAP and to assess ways to improve the quality and value of the clinical efficacy and safety data derived from future studies. The FDA is concerned about the validity of noninferiority studies in the assessment of efficacy of new drugs for CAP. Industry is concerned about the feasibility of untested study designs. Although these positions may appear to be in opposition, there are ways to improve the design of industry-sponsored studies without jeopardizing the ability to conduct such trials.

CAN CLINICAL TRIALS BE IMPROVED?

CAP studies present 3 fundamental issues. First, can the selection of a microbiologically valid population (i.e., the modified intention-to-treat population) be improved? Second, which clinical outcomes should be used as primary or secondary end points? Third, what degree of statistical veracity do we apply to these end points and their populations?

The diagnosis of a specific microbiological etiology for CAP by use of standard culture methods is decidedly inadequate in the majority of cases. The serological identification of atypical bacterial pathogens requires convalescent-phase samples and is
untimely for clinical decision making. Urinary antigen tests are available for S. pneumoniae and Legionella pneumophila and are now used in clinical trials for CAP. However, these urinary antigen test methods, in addition to conventional culture techniques, result in a microbiological diagnosis in <35% of the overall population of hospitalized patients with CAP, on the basis of recent clinical trials (table 1) [15, 16]. The promising technique of PCR detection of typical bacterial pathogens is an additional method for detection of the etiology of CAP. Once these new diagnostic methods have received regulatory approval, they may be used to further document the causative pathogens and to enhance the microbiologically evaluable population. Although the technology of PCR may not provide a rapid “bedside” diagnosis, it is suitable for inclusion in multicenter clinical studies.

It has been proposed that biomarkers, such as C-reactive protein and procalcitonin, can aid in the screening of patients by differentiating bacterial from nonbacterial CAP in the community setting. However, caution is required; a “sensitive” procalcitonin assay was neither sensitive nor specific in a recent trial of acute otitis media [17]. Moreover, Holm et al. [18] evaluated both procalcitonin and C-reactive protein as possible predictors of pneumonia in the primary care setting and reported that positive predictive values were too low to be accurate predictors for both markers.

Physician clinical assessment has been the primary outcome parameter used for efficacy in all recent CAP studies used to support New Drug Applications. The FDA’s concern about this point-in-time assessment is 2-fold: there is great variability among investigators in their global assessment, and the assessment of clinical response at a single point in time after treatment may not be sensitive enough to distinguish between treatments. For other indications, including such non–life-threatening infections as acute bacterial sinusitis and acute otitis media, the use of patient-reported outcomes is suggested as an alternative primary outcome measure [19]. Lamping et al. [20] developed a patient-oriented questionnaire, which has undergone various stages of validation for CAP; however, it is not a validated FDA-standard patient-reported outcome. Its use in a clinical CAP study that compared 2 approved therapies did not demonstrate an enhanced ability of patient-reported outcomes to differentiate between treatments beyond that of conventional physician assessment [21]. Indeed, the authors commented that this new patient-derived assessment “was complementary [to standard physician clinical assessment] in the evaluation of disease treatment” [21, p. 141]. A similar result was found in another CAP study that used a different assessment tool [22]. Although such patient-derived response instruments may add to the depth of the outcomes measured in future clinical studies, they have not proven to be a better outcome measure than physician assessment, at least for CAP.

The most troubling issue regarding CAP studies is the basis for justification of the noninferiority margin. The apparent benefit of antibiotics for treatment of CAP was established in the 1930s, when a series of studies and clinical experiences showed a sizeable reduction in pneumonia-related mortality. The treatment effect was so substantial that subsequently it was considered unethical to withhold antimicrobial treatment; consequently, there are no recent placebo-controlled studies of CAP involving typical bacterial pathogens. Although mortality may be an appropriate outcome measure for more-severe CAP treated with parenteral antibiotics in the hospital, mortality is not a suitable primary outcome parameter for noninferiority studies of mild-to-moderate CAP among outpatients given treatment with oral therapy. Does the absence of previous placebo-controlled studies of CAP mean that superiority studies, either placebo controlled or active drug controlled, will be necessary for future drug approval for CAP? Such a regulatory position would greatly discourage any industry sponsor. Perhaps such a study should be conducted by the National Institutes of Health in a highly controlled environment, to guarantee patient safety. We think that there are other ways to justify a noninferiority margin on the basis of historical and contemporary studies that use clinical response, not mortality, as the outcome parameter [16].

The pharmaceutical industry understands that the FDA is grappling with these study design issues. Both individual companies and the Pharmaceutical Research and Manufacturers of America have contributed their thoughts and shown a willingness to work with the FDA to address the deficiencies of studies conducted under the previous FDA guidelines. Clearly, the introduction of new diagnostic methods that allow the identification of bacterial pathogens is appropriate and is best done in large, multicenter studies. The utilization of alternative outcome measures can also be incorporated into studies whose

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Table 1. Microbiological yield in randomized clinical trials for community-acquired pneumonia in hospitalized patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of patients</th>
</tr>
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<tbody>
<tr>
<td>Total enrolled</td>
<td>748</td>
</tr>
<tr>
<td>Total randomized</td>
<td>738 (98.7)</td>
</tr>
<tr>
<td>Total valid for safety and/or ITT analysis</td>
<td>733 (98.0)</td>
</tr>
<tr>
<td>Total per-protocol population</td>
<td>569 (76.1)</td>
</tr>
<tr>
<td>With pneumococcal pneumonia</td>
<td>162 (21.7)</td>
</tr>
<tr>
<td>With Streptococcus pneumoniae isolated</td>
<td>77 (10.3)</td>
</tr>
<tr>
<td>With atypical pathogens identified by serological analysis</td>
<td>86 (11.5)</td>
</tr>
<tr>
<td>Infected with Legionella pneumophila</td>
<td>22 (2.9)</td>
</tr>
<tr>
<td>Infected with Haemophilus influenzae</td>
<td>18 (2.4)</td>
</tr>
<tr>
<td>Infected with Staphylococcus aureus</td>
<td>8 (1.1)</td>
</tr>
</tbody>
</table>

NOTE. ITT, intention to treat. Data are from [15].

a S. pneumoniae was isolated by blood or respiratory cultures and/or was identified by positive results of urinary antigen testing.

b Identified by urinary antigen test.
primary purpose is to gain approval of new drugs. However, these outcome measures should remain secondary parameters and should not be the basis for drug approval, until they are validated in a true clinical trial setting. The above-mentioned changes should be considered evolutionary steps in the context of otherwise-feasible study designs. If, however, there is a requirement of superiority trials for CAP, either placebo controlled or active controlled, the technical risk of the study design, not the investigational drug, becomes the overriding issue for the sponsors. It is our opinion that the increase in risk would preclude any sponsor from pursuing such “experimental” study designs for a new antibiotic. The evolution of improved trial design would cease. This is not in anyone’s best interest.

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References

15. Torres A. To determine the efficacy and safety of moxifloxacin monotherapy in hospitalised patients with CAP (PSI risk classes III–V) [abstract 1061]. In: Program and abstracts of the 16th European Congress of Clinical Microbiology and Infectious Diseases (Nice), Basel, Switzerland: European Society of Clinical Microbiology and Infectious Diseases, 2006.