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Re: New Approaches to Antibacterial Drug Development,  
Docket Number: FDA-2013-N-0556

Dear Drs. Hamburg and Woodcock:

The National Physicians Alliance (NPA), a national organization of more than 15,000 physicians representing multiple medical specialties that promotes high quality health care, and Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, welcome the opportunity to comment on Federal Register notice FDA-2013-N-0556 regarding New Approaches to Antibacterial Drug Development.

The mission of the Food and Drug Administration (FDA) is to protect the public health, primarily by assuring the safety and efficacy of drugs, biologics, and other therapeutics (1). Day after day in our clinics and hospitals, we increasingly see patients suffering

from infections caused by resistant pathogens. This public health crisis can be addressed through appropriate use and stewardship of antimicrobials, infection control strategies, immunization and other disease prevention measures, and the development of rapid point of care diagnostics that might limit the unnecessary use of antibiotics, as well as approval of safe and effective interventions based on adequate and well controlled trials.

Recently, however, several publications authored by stakeholders from academia and the pharmaceutical industry have urged the FDA to reduce the evidentiary standard required for marketing approval of antibacterial therapies in an effort to increase the number of available new drugs (2, 3). FDA has proposed adopting many of these changes (4-6), as outlined in the FDA Draft Guidance “Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases” (7). Adopting these changes would not meet the stated goal of combatting antimicrobial resistance, but would instead result in the approval and widespread use of drugs that are ineffective or less effective than existing therapies, placing patients at risk and providing a disincentive for companies to develop more effective agents. Recent history points to the dangers of inappropriate clinical trials standards: the FDA has approved over 60 New Drug Applications for drugs to treat acute otitis media, acute bacterial sinusitis, and acute exacerbations of chronic bronchitis based on non-inferiority trials. Even the FDA has acknowledged that this study design cannot reliably distinguish effective drugs from placebo (8), and some of these drugs have been linked to an increased risk of serious, sometimes fatal, adverse events (9, 10, 11). The consequences of inappropriate trial designs in the setting of life threatening diseases are even more severe – death from ineffective treatments when effective therapies exist. FDA has released warnings regarding drugs that have increased deaths in serious and life –threatening diseases when approved through non-inferiority trials using outcomes other than mortality (12, 13).

Rather than simply approve more drugs, the goal is to approve medications that are effective and safe, which is demonstrated with robust, reproducible evidence from adequate and well-controlled clinical trials. This is the scientific standard for evaluating the effectiveness of a drug, as described in law, legal precedent, current US federal regulations (14) and international regulatory standards accepted previously by pharmaceutical companies (15,16). Therefore, based on FDA’s statutorily defined regulation on the conduct of adequate and well-controlled trials, we wish to make the following comments regarding the evaluation of therapies for the treatment of serious and life threatening diseases:

1. **Trials should have a clear objective based on a well-defined patient population.** Although it was common practice in the 1970’s and 1980’s to study antibacterial drugs in heterogeneous patient populations with infections due to the same pathogens at anatomically unrelated sites, this drug development strategy was discarded a quarter-century ago based on well-recognized scientific principles. Trials that pool patients with infections caused by the same pathogen but occurring at different anatomic sites into a single study cannot provide clinicians or patients with adequate

evidence about safety and effectiveness in those diseases, because patient characteristics, natural history of disease, antimicrobial pharmacokinetic and pharmacodynamic properties, and response to therapy can differ even if the diseases are caused by the same pathogen. For instance, a recent trial that pooled different infections due to a single multi-drug resistant pathogen enrolled only 5 patients (2.9% of the total enrolled) with intra-abdominal infections, an insufficient number to draw any conclusions regarding efficacy in this disease (17). FDA's own recent experience has shown that drugs have different effects at different body sites such as the failure of daptomycin in the treatment of community-acquired pneumonia (18).

2. **Approval of new drugs for patients with unmet medical needs should be based primarily on studies that enroll patients who have the unmet medical needs.** Findings from non-inferiority trials enrolling less seriously ill patients with infections from drug-susceptible pathogens cannot answer the question of whether a new drug provides benefits that outweigh risks in sick patients with disease due to resistant pathogens and raises ethical issues about exposing patients who have options to excess harm.

3. **Studies to evaluate new drugs intended for patients with unmet medical needs should be superiority trials, because they provide direct evidence about the benefits and harms of new drugs.** The Draft Guidance attempts to outline circumstances under which non-inferiority studies could provide evidence of effectiveness for patients with the unmet medical need of serious bacterial infections (7). However, when well-designed and rigorously conducted, non-inferiority study designs at best can only rule out how much worse a new therapy might be compared with an older drug that already meets the medical need of the patient population studied. Superiority trials also offer the advantage of smaller sample sizes and less potential for bias when compared with non-inferiority trials, and contrary to claims from industry, superiority trials are also feasible in the setting of serious disease due to resistant pathogens (17).

4. **Studies that provide evidence of clinical efficacy should have baseline comparability between treatment groups, which is accomplished by randomization.** Expedited programs for the drug approval have been described, both for antibacterial therapies (7) and for drugs and biologics more generally (8), which would allow evidence from studies that make use of external or historical control groups -- in other words, non-randomized observational studies. While observational studies can provide important information about the unintended effects of medications and identify serious treatment limiting or life-threatening toxicities (19,20), they are unsuitable study designs for efficacy determinations due to the often insurmountable potential for confounding (21-23) and overestimation of treatment effects (24). Although permitted in a few rare circumstances in current FDA regulations, observational non-randomized studies are not a compelling basis for determining the efficacy of new antibacterial therapies in patients with infections due to resistant pathogens.

5. **The FDA should require two randomized controlled trials for the approval of a new antibacterial therapy in nearly all instances.** Replication, or reproduced findings in two independent studies, is important not only for drug approval but in science more generally (25), and it addresses both problems of type I error (false positive findings) (26) and systematic bias that can occur in any single study. For example, drotrecogin alfa (recombinant human activated protein C) was approved for the treatment of severe sepsis on the basis of a single Phase 3 trial, which was stopped early because of a reduction in mortality associated with drotrecogin alfa at a pre-specified interim analysis (27). The drug was approved in 2001 despite concerns about previous failed attempts to reproduce results of sepsis clinical trials (28). Three large sepsis clinical trials in adults and children failed to replicate the initial positive findings, and the drug was eventually withdrawn from the market by the manufacturer (27,29-31). Two studies should be required when drugs are approved through non-inferiority trials as these studies do not meet an unmet medical need and are subject to numerous biases which can affect their validity. Although two clinical trials for the same disease would provide the most convincing evidence of efficacy for a proposed indication, two trials in similar but distinct diseases – such as community acquired bacterial pneumonia and hospital acquired pneumonia, or hospital acquired pneumonia and ventilator associated pneumonia – could provide robust findings of efficacy adequate for regulatory approval.

6. **Evidence of effectiveness must come directly from well-designed human studies, and should *not* be inferred from *in vitro*, animal, and pharmacokinetics studies.** Some have suggested that a single randomized controlled trial can provide sufficient evidence of efficacy, in combination with small pharmacokinetics or animal studies, so-called “casual evidence” (6,32). While these study designs provide important information about the mechanism of therapeutic effects, establish optimal drug dosing, and identify potential toxicities at an early stage in the development of a drug, they cannot replace adequately powered Phase 3 trials designed to establish the efficacy of a drug in human subjects. Indeed, the strong biologic plausibility of a therapeutic effect of drotrecogin alfa in the treatment of severe sepsis on the basis of animal studies demonstrating the role of activated protein C in promoting fibrinolysis and inhibiting thrombosis and inflammation did not protect against a false positive result from the initial Phase 3 trial (33). Antibacterial drugs like doripenem in hospital-acquired pneumonia had promising *in vitro* and animal studies and even when dosed according to “optimized” pharmacokinetic modeling still increased mortality (34). In part because of the complex genetic makeup of human populations and the varied context of human disease, findings from animal studies often do not generalize to humans (35, 36)

7. **Outcomes in clinical trials should be direct measurements of irreversible morbidity or mortality, or patient-centered outcomes.** Trials that evaluate surrogate endpoints rather than appropriate outcomes often overestimate treatment effects or suggest an effect when one does not exist (37), and sometimes fail even when the surrogate endpoint is seemingly well-validated with other drugs and in other settings (e.g., low density lipoprotein and coronary heart disease, CD4 counts in HIV interleukin-2 studies) (38, 39). Furthermore, patients with serious and life threatening infectious

diseases often die at a high rate in a short period of time. Therefore, there is no rationale for evaluating surrogate endpoints in the setting of acute, life-threatening diseases. The need to focus on irreversible morbidity or mortality rather than surrogate endpoints such as the poorly-defined and subjective “clinical response” is illustrated by tigecycline. Although this antimicrobial was approved on the basis of findings from non-inferiority studies that evaluated clinical response, a pooled analysis of clinical trials found that tigecycline was associated with a higher mortality rate than comparable antimicrobials (12,13). As another example, televancin was approved for the treatment of hospital-acquired pneumonia on the basis of two non-inferiority trials, despite increased risk of death in one of the studies while showing non-inferiority on “clinical response” (40).

**8. Trials should use appropriate methods of statistical analyses.** Bayesian methods that use prior likelihoods based on positive results from animal or small clinical studies, or that include only effective drugs while ignoring failed drugs, are likely to result in bias and overestimate treatment effects for new therapies. Despite promising results from *in vitro*, animal model, and pharmacokinetics studies, a number of antibacterial therapies have failed to demonstrate benefits for patients when evaluated in appropriate human studies, and some may result in an increased risk of death, either due to ineffectiveness or toxicity. There are several recent examples: doripenem for the treatment of hospital-acquired and ventilator-associated pneumonia (34), cethromycin for the treatment of community-acquired bacterial pneumonia (41), and tigecycline (12,13). “Descriptive” statistics (6) are entirely inappropriate for evaluating the effectiveness of drugs and FDA should insist on scientifically valid statistical methodologies when evaluating new therapies

**9. Adequate evidence of safety is necessary before marketing approval of any new drug can be granted.** This is especially true when the new drug is studied in non-inferiority trials, where improvements in safety or tolerability provide the primary rationale for regulatory approval. Current and future patients who already have safe and effective treatment options should not be placed at increased risk from less effective therapies. This violates the principle of Justice in the Belmont Report regarding the equitable distribution of the benefits and risks of clinical research (42).

**10. Continued discussions about existing FDA guidance for antibacterial drugs divert important resources from other important areas of the FDA’s mission.** Appropriate guidance for clinical trial design is already contained in international guidances accepted by FDA, international regulators and pharmaceutical companies (15,16). There are over 30 guidance for antimicrobials (43) compared to seven for all cancers combined (44). Approvals for cancer drugs have increased showing that numerous guidances are neither synonymous nor needed for innovation. Any new guidances should not violate FDA regulations or principles contained in law, regulation and internationally accepted guidances (15,16).

The concept of “first do no harm” has been a basic tenet of medicine for thousands of years. Offering patients therapeutic “options” when safety or effectiveness is unclear

does not help patients or aid clinicians in treating patients appropriately. Furthermore, an unmet medical need is not a reason to accept a lower standard of evidence from clinical trials for potential new therapies. Even in the pre-antibiotic era, when no effective treatments for infections were available, investigators understood the need for adequate and well-controlled trials (45). Additionally, proposals to accelerate approval for promising new therapies based on limited evidence of efficacy require both ongoing robust evidence development after approval and restrictions on marketing (46). However, the off-label use of medications in the U.S. is common across a variety of settings and geographic distributions (47-49), and the expectation that new antibacterial therapies will not be used more broadly than indicated is neither practicable nor supported by evidence. Indeed, the overuse of antibacterial therapies by clinicians is a major driver of growing problem of infections due to resistant pathogens. Even if drugs are used off-label by clinicians this is an entirely different issue than allowing drug companies to advertise unstudied uses of their products. Recently, the US government has fined pharmaceutical companies for off-label marketing of drugs including antibiotics on numerous occasions (50).

The FDA has a critical role in protecting public health. It provides assurance to physicians and patients that new therapies are both safe and effective before they become available for widespread use. Fulfilling this role can be difficult in the face of pressure to erode the current regulatory standard (5, 6). Current FDA policies that require robust and reproduced scientific evidence of efficacy and safety from independent randomized clinical trials are not merely “regulatory barriers” to be circumvented -- they are regulatory standards that are well grounded in science and have protected the health of the public for several decades. We welcome further discussion and will elaborate on our comments at the request of the FDA.

Sincerely,



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