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The potential risks of expedited approval of drugs for acute bacterial infections

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Each year, about 23,000 people in the United States die from antibiotic-resistant infections. For many of these infections, safe and effective treatments are lacking. To address this problem, the Food and Drug Administration (FDA) has updated several expedited approval programs for new antibacterial therapies, some of which alter the evidentiary standard for drug approval.^{1,2} For instance, a drug may be eligible for “accelerated approval” if it “has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit.”² Since 1992, the accelerated approval program has been available for drugs likely to offer a therapeutic benefit over available treatments for serious or life-threatening diseases. Now, the program’s scope has been expanded to include drugs with marginal ancillary benefits such as a novel mechanism of action without improvements in safety or efficacy. These well-intentioned new standards for accelerated drug approval have increased the risk that the agency will approve antimicrobials that are less effective or more harmful than available treatments.

The FDA first developed regulations on the use of surrogate endpoints for accelerated approval in response to the human immunodeficiency virus (HIV) epidemic, at a time when there were few effective treatments and patients developed opportunistic infections and died soon after their illness progressed. Early HIV drugs were approved on the basis of trials that evaluated both health outcomes and surrogate endpoints. These studies provided evidence that an increase in the CD4 cell count did not reliably predict meaningful health benefits from treatment with a single antiretroviral medication.³

After reliable assays of viral load became available, studies demonstrated that large and durable drug effects on viral load predicted reductions in life-threatening infections and deaths. Viral load became an accepted surrogate for the effect of antiretroviral drugs on HIV infection, allowing experimental agents to be evaluated in relatively small and short-term trials and the FDA to approve drugs more rapidly than if trials had evaluated only clinical endpoints.

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For acute bacterial infections, trials based on surrogate endpoints may be less informative. For example, ventilator-associated bacterial pneumonia is a serious infection among hospitalized patients that is often caused by highly resistant pathogens, such as carbapenem-resistant gram negative bacteria. In contrast to HIV, effective therapies for ventilator-associated bacterial pneumonia substantially reduce short-term mortality. In a meta-analysis of clinical trials and observational studies, the in-hospital or 28-day mortality rates among patients who received inadequate, delayed, or inappropriate treatment were 60% (95% confidence interval [CI], 49%–69%), compared with 20% (95% CI, 18–23%) for patients who received recommended therapy.⁴ For severe bacterial infections with high short-term mortality, evaluating a surrogate endpoint rather than mortality would not allow clinical trials to be shorter and smaller.

In trials of medications for pneumonia, composite endpoints have included various biomarkers, such as blood oxygenation, body temperature, and the results of imaging studies. Although changes in such measures may correlate with symptom resolution or prolonged survival, evidence is lacking that antibiotic effects on these potential surrogates reliably predict important health benefits for patients. In the absence of such evidence, since 2010 the FDA has recommended mortality as the primary endpoint in ventilator-associated bacterial pneumonia trials.⁴ However, the new expedited approval pathways may have opened the door for future drug approvals based on surrogate endpoints. The approval of the antimicrobial telavancin highlights the potential difficulties of this approach.

In June 2013, the FDA approved telavancin for the treatment of nosocomial pneumonia based on results from two non-inferiority trials conducted in patients with ventilator-associated and hospital-acquired bacterial pneumonia. In a non-inferiority trial, the efficacy of an experimental drug is established by excluding a clinically acceptable loss of efficacy of an active control drug, using historical evidence of the control drug efficacy. The primary outcome in both trials was “clinical response,” a composite endpoint that included both indirectly-measured elements of patient benefit (physician-reported symptoms) and biomarkers (physical signs, imaging findings, and blood oxygenation). Telavancin was determined to be “non-inferior” because both trials excluded a 10% lower rate of clinical response with telavancin compared with vancomycin (Table).⁵

In the trial that enrolled sicker patients (Study 0015), however, telavancin was associated with an increased risk of death (risk difference 5.8%; 95% CI, –0.3 to 11.9%) and serious renal adverse events (risk difference 2.7%; 95% CI, 0.2 to 5.2%). Thus, for telavancin, a drug with no clear ancillary benefits, such as improved safety or convenience, an evaluation of the surrogate endpoint of clinical response provides a different picture of the drug’s risk-benefit profile than an evaluation of mortality. On the basis of these findings, telavancin was approved for the treatment of *Staphylococcus aureus* ventilator-associated pneumonia, when alternative treatments are not suitable, a poorly-defined population that was not studied.⁵

Surrogate endpoints have also been used to assess therapies for serious skin and soft tissue infections. In March 2014, the FDA Anti-Infective Drugs Advisory Committee discussed tedizolid and dalbavancin, two antimicrobials granted priority review status under the Generating Antibiotic Incentives Now Act.⁶ Each new drug was compared with an existing

therapy (vancomycin or linezolid) in two non-inferiority trials. Each of these trials excluded a 10% lower rate of clinical response, defined as a 20% reduction in lesion size within 48–72 hours, with the new antimicrobial compared with the control drug. Mortality rates, regardless of the drug used, were 1% or lower.

Non-inferiority trials are most informative when there is robust evidence of effectiveness for the active control drug. For skin and soft tissue infections, such evidence comes from two non-randomized studies, published in 1937, that compared sulfa drugs with ultraviolet light for the treatment of streptococcal skin infections.⁷ Symptoms were not reported and there was no effect on mortality or complications. The greatest effect of treatment was an early reduction in lesion size, a biomarker that may not capture the health benefits of antibacterial therapy, such as symptom improvement. Moreover, the effects of sulfa drugs in studies conducted 80 years ago may not be relevant to the recent trials, where *Staphylococcus aureus* accounted for 80% of isolated pathogens and the active control drugs were linezolid and vancomycin.

Although treatments for acute bacterial infections with high short-term mortality are now eligible for accelerated approval, there is little need for surrogate endpoints and no well-validated ones exist. For less severe infections, direct benefits of new antimicrobials on patient symptoms and function are uncertain when assessments rely on surrogate endpoints. This uncertainty is compounded by non-inferiority study designs, which establish efficacy indirectly by using historical evidence. The FDA could require confirmation of clinically meaningful benefits through post-marketing trials that assess important health outcomes. However, even when companies fulfill post-marketing commitments, it can be nearly impossible to remove a drug from the market because of pressure from the manufacturer, professional organizations, and patients.⁸

To assess new treatments for drug-resistant bacterial infections, superiority trials that enroll patients with these infections are the optimal study design; such trials can identify clinically meaningful benefits with modest sample sizes. For example, a recent trial enrolled 210 patients with serious *Acinetobacter baumannii* infections susceptible only to colistin, a highly toxic drug approved before the FDA began to require evidence of efficacy for medications in 1962. The intervention in this study, the addition of rifampicin to colistin, was not effective and 90 patients in the study died within 30-days. With this 43% mortality rate in a control group, treating only 90 patients with a novel antibiotic would provide greater than 80% power to detect an absolute mortality reduction of 20%.⁹

The problem of resistant bacterial infections requires solutions that extend beyond changes in the evidence standards for regulatory approval. Efforts to decrease inappropriate antibiotic prescribing by healthcare providers¹⁰ and to limit use in livestock can help to prevent drug resistance in the first place, and prolong the usefulness of existing therapies. Economic incentives, improved diagnostics for bacterial infections, and advances in genomics may facilitate the development of new therapies. Although lowering scientific standards in programs for expedited drug approval is likely to increase the number of antimicrobials on the market, this approach may have little impact on the public health

burden of resistant bacterial infections and instead may increase the availability of some ineffective or harmful therapies.

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Table 1
Phase 3 trials of Telavancin reviewed by the FDA Anti-Infective Drugs Advisory Committee.⁵

Endpoint	Study 0015			Study 0019		
	Telavancin arm, N (%)	Vancomycin arm, N (%)	Risk difference (95% CI)	Telavancin arm, N (%)	Vancomycin arm, N (%)	Risk difference (95% CI)
Clinical Response	214/372 (57.5%)	221/374 (59.1%)	-1.6% (-8.6 to 5.5%)	227/377 (60.2%)	228/380 (60.0%)	0.2% (-6.8 to 7.2%)
Mortality, day 28	95/372 (25.5%)	74/374 (19.8%)	5.8% (-0.3 to 11.9%)	83/377 (22.0%)	90/380 (23.7%)	-1.9% (-8.0 to 4.2%)

Results were taken from advisory committee meeting briefing documents. Clinical response was defined as signs and symptoms of pneumonia improved to the point that no further antibacterial drugs for pneumonia were required, and baseline radiographic findings improved or did not progress. CI = confidence interval.