

Regulating Antibiotics in an Era of Resistance: The Historical Basis and Continued Need for Adequate and Well-Controlled Investigations

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Two bills introduced in Congress (the Promise for Antibiotics and Therapeutics for Health Act and the Antibiotic Development to Advance Patient Treatment Act of 2013 in the 21st Century Cures Act) propose changes in the regulatory approval of new antibiotics in the context of attempts to reengage industry amidst fears of a postantibiotic future. Despite anti-infectives having among the shortest development times and highest approval rates among therapeutic classes (1-3), some propose that the requirements of adequate and well-controlled studies make the study of new antibiotics infeasible (4). To address perceived hurdles, these bills propose a regulatory pathway in poorly defined "limited populations" without requiring demonstrated benefits in populations with resistant disease. Studies would be done in patients with effective options rather than those with unmet medical needs, allowing approval even with inferior effectiveness in the population studied. No requirement for diagnostics means that the drugs may be prescribed empirically outside the limited population. The bills would alter the standard of approval from substantial evidence to "sufficient evidence" derived from "small clinical data sets" and would consider preclinical data, animal models, and pharmacologic data to be "confirmatory evidence." In the setting of such proposals, historical reflection is in order.

Antibiotics were the leading example of post-World War II "wonder drugs," dramatically rebranding medicine. They were the most lucrative segment of the pharmaceutical industry and transformed such companies as Pfizer and Parke-Davis. Yet, despite the advent of penicillin and broad-spectrum antibiotics, by the early 1950s staphylococcal resistance led to the perceived need for an arms race to keep up with life-threatening diseases caused by resistant organisms (5).

By the mid-1950s, pharmaceutical companies marketed antibiotic combinations, predicated on in vitro synergy, as solutions to resistant organisms. However, leading infectious disease researchers, including Maxwell Finland, Harry Dowling, and Ernest Jawetz, found them to be no more effective than their components in treating human disease; strain-dependent in their action; and, hence, not amenable to prepackaged formulations. Despite these observations, the drugs were widely promoted and used in what Finland and Dowling perceived as an evidentiary vacuum. At the time, the U.S. Food and Drug Administration (FDA) could only formally adjudicate drug safety (not efficacy), and to Finland and Dowling, the widespread marketing and uptake of these antibiotics, based on what they termed "testimonials" (case series supported by in vitro

data), portended a future of style over substance that threatened the very future of rational therapeutics (5).

In response, Finland called for controlled clinical trials to offset premature claims of efficacy. In 1957, he wrote on behalf of 18 leading infectious disease researchers (6):

To be sure, properly conducted clinical studies may, in the future, support the claims and justify the enthusiasm for these or other . . . antimicrobial agents, but it is incumbent upon those of us who are intimately concerned with the welfare of our patients to wait until such data are presented before we accept and acclaim any new agents or special formulations and recommend them for general use, particularly in view of their great potential for harm when they are used extensively and indiscriminately.

Finland's concerns were echoed by a 1959 article in the *Saturday Review*, "Taking the Miracle Out of the Miracle Drugs" (7). Antibiotics received prominent attention when Senator Estes Kefauver launched his investigation of the pharmaceutical industry later that year, and with the passage of the Kefauver-Harris amendments in 1962, all new drugs were required to be found efficacious on the basis of "adequate and well-controlled investigations."

After passage of the amendments, the FDA commissioned the Drug Efficacy Study, which reviewed drugs approved between 1938 and 1962. By 1969, the FDA attempted to remove certain antibiotics lacking substantial evidence of efficacy from the market. Upjohn's multimillion-dollar drug Panalba (a combination of tetracycline and novobiocin) became the test case. Its use had been justified on the basis of what the company called "the totality of the materials"—in vitro data, animal studies, and poorly controlled human studies—but not the modern methods of controlled studies that were to form the new evidentiary standard (8). The FDA carefully delineated the new standards for "substantial evidence" from "adequate and well-controlled investigations," with the randomized, controlled study to serve as the ideal. The courts affirmed the legality of the FDA's actions, thus enforcing the placement of the rigorously conducted controlled trial at the center of drug evaluation and regulation (5, 9).

The current concerns about worsening antibiotic resistance would sound familiar to Finland and Dowling (the first and third presidents, respectively, of the Infec-

Table. Recent Examples of FDA-Approved Antibiotics With Evidence of Increased Mortality and/or Decreased Effectiveness Compared With Older Drugs in Relevant Populations in Randomized Trials Despite Promising Preclinical and Early Clinical Data

Drug	Disease	Data
Daptomycin	Community-acquired pneumonia	Decreased effectiveness compared with ceftriaxone; found to bind to surfactant in lungs after adequate and well-controlled trials completed; approved for complicated skin and skin structure infections and <i>Staphylococcus aureus</i> bloodstream infections (bacteremia) (10)
Tigecycline	Hospital-acquired pneumonia, intra-abdominal infections, and skin infections	Increased overall mortality compared with older antibiotics in meta-analysis (11); approved for complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia
Doripenem	Hospital-acquired pneumonia	Study stopped early because of increased mortality compared with imipenem in hospital-acquired and ventilator-associated pneumonia despite optimized pharmacodynamic dosing; approved for complicated intra-abdominal and complicated urinary tract infections (12)
Telavancin	Hospital-acquired and ventilator-associated bacterial pneumonia	Increased mortality compared with vancomycin in hospital-acquired and ventilator-associated bacterial pneumonia in patients with renal insufficiency; increased risk for renal insufficiency (13); approved for complicated skin and skin structure infections and hospital-acquired and ventilator-associated bacterial pneumonia when alternative treatments are not suitable (but not studied in this population)
Ceftazidime-avibactam	Complicated intra-abdominal infections and complicated urinary tract infections	Decreased effectiveness compared with meropenem or imipenem in complicated intra-abdominal and complicated urinary tract infections in patients with renal insufficiency; approved on the basis of 2 studies with no hypotheses for inferential statistical testing against active comparators for complicated intra-abdominal infections (in combination with metronidazole) and complicated urinary tract infections in patients who have limited or no treatment options (but not studied in this population) (14)

FDA = U.S. Food and Drug Administration.

tious Diseases Society of America). However, they might be surprised to see current bills suggesting the same kind of evidence that was rejected by the FDA with Panalba. As in Finland's time, current evidence shows that this information—termed “totality of the evidence” and echoing Upjohn's “totality of the materials” proposed with Panalba—is hypothesis-generating and is not confirmatory of effectiveness in human disease. Recent antibiotics with promising in vitro data, animal models, and pharmacometrics have shown increased mortality or decreased effectiveness compared with older drugs in randomized trials in sicker patients, as well as differences in outcomes in sicker patients and across diseases (Table). In a reversal of antibiotics as the test case for rigorous trial methodology, proposals now call for expanding approvals based on preclinical data to all other therapeutic areas.

Rather than using “modern” methods, some current proposals advocate methods shown in Finland's time to be unable to separate helpful agents from harmful ones. Finland and colleagues experienced firsthand the need for better treatments in the face of resistance yet still called for adequate and well-controlled trials as the solution—not the problem—to ensuring a rational therapeutics. More recently, other bills have been introduced that seek to maintain the scientific standard that has defined the antibiotic era (15).

The controlled clinical trial was developed relatively recently in the history of medicine. Investigators

developed this methodology to protect patients. As Finland stated: “Clinical investigators and authors of medical and scientific publications [have] the duty to protect the medical profession and the public against the abuse of preliminary scientific information and against the improper and premature exploitation of conclusions based on inadequate data” (6). The past reminds us that present patient safety and rigorous evaluations of drug effectiveness should still be considered along with uncertain depictions of the future.

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