FDA Approval Process Hinders Development of New Antibiotics  
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There are two broad categories of clinical trials used to determine if a new drug should be approved by the United States Food and Drug Administration (FDA): superiority trials and non-inferiority trials. There are two forms of superiority clinical trials. In one form, the experimental drug is compared with placebo (“placebo controlled study”). Placebo-controlled superiority studies cannot be conducted for patients with serious bacterial infections, because it is unethical to knowingly administer placebo to such patients.

In the second form of superiority study, the experimental drug is compared with another drug already on the market. An experimental antibiotic that can kill bacteria that are resistant to a comparator antibiotic should have superior efficacy to that comparator antibiotic when treating patients infected with those resistant bacteria.

However, since patients infected with bacteria that are resistant to the comparator antibiotic cannot ethically be randomized to a chance of being treated with that comparator antibiotic, the comparator antibiotics used in clinical trials are specifically selected to be active against almost all bacteria likely to infect patients enrolled in the study. When comparing two antibiotics, both of which kill all the bacteria causing infections in enrolled patients, it is highly unlikely that one antibiotic is going to be superior in efficacy to the other. Such studies pose an unacceptable risk of failing to show that that the experimental drug is superior to the comparator drug, even if the experimental drug is, in fact, highly effective.

Since superiority studies cannot be conducted for most serious infections, the only possible pathway to approval for many new antibiotics is the conduct of a “non-inferiority” clinical trial, which seeks to determine if the experimental drug is similar in efficacy to a standard drug already on the market. For the last few years, the United States Food and Drug Administration (FDA) has been reconsidering the standards it uses to judge so-called “non-inferiority” clinical trials, which seek to determine if an experimental drug is similar in efficacy to a standard drug already on the market. If the experimental drug is found to be “non-inferior” to the comparator drug, there are two possible statistical interpretations: 1) both drugs are superior to placebo for the disease under study, and the experimental drug should be approved by the regulatory agency; OR 2) neither drug is superior to placebo for the disease under study, and the reason why the drugs appear to have similar efficacy is that a similar placebo-effect is seen in both arms. Approval of the experimental drug under the latter scenario would result in marketing of an ineffective drug to the public.

The following is a simple logic flow the agency can use to ensure that ineffective drugs are not approved as a result of successful non-inferiority studies:

1) If the comparator drug is known to be superior in efficacy to placebo from prior studies  

AND

2) the experimental drug is similar in efficacy to the comparator drug
3) the experimental drug must also be superior in efficacy to placebo

By this logic, non-inferiority clinical trials should only be used when the comparator drug has been previously shown to be superior to placebo. Unfortunately, this desire for previous randomized placebo-controlled trials, while logical, is also the fundamental underpinning for why antibacterial development, out of proportion to other drugs, has been so severely impacted by the current regulatory environment. Antibacterial agents were among the first effective drugs used in Western medicine, and became available in the US in late 1936, fully 20 years before randomized placebo-controlled trials came into widespread use. Thus, for virtually all serious infections, there are no randomized, placebo-controlled studies to define how effective comparator antibiotics are, which makes problematic the design of modern non-inferiority studies for these diseases.

Nevertheless, less sophisticated studies from the 1930s-1940s unequivocally document a massive survival benefit of antibiotics for serious bacterial infections. Overall, the rate of death from infections in the US fell by ~220 per 100,000 population during the first 15 years of the antibiotic era; that rate of death then fell only by a further ~20 per 100,000 over the following 45 years, during which time all other advances in modern medicine (including critical care medicine) were achieved. There is no question that antibiotics are life-saving for serious bacterial infections.

It has also been argued that we should simply stop doing non-inferiority trials because what we really want are “better” drugs, not “non-inferior” drugs, to treat antibiotic resistant infections. As discussed earlier, though, patients in whom a new drug is likely to be superior to an old drug are those infected by bacteria resistant to the old drug who cannot ethically be enrolled in the clinical trial, since they cannot be randomized to a chance of receiving ineffective treatment. For example, when studying a new antibiotic with efficacy against methicillin-resistant Staphylococcus aureus (MRSA), one cannot randomize patients infected with MRSA to a 50% chance of being treated with methicillin. Instead one has to compare a new antibiotic to an old antibiotic for the treatment of infections susceptible to both drugs. In these comparisons, the new drug is very unlikely to be superior to an effective old drug, making such studies impractical.

Sufficient data are available to ensure that comparator antibiotics used in non-inferiority studies for new antibiotics are massively more effective than placebo. Because we can be certain that antibiotics did have very large treatment effects for serious bacterial infections and because superiority studies of antibacterial agents are impractical in most cases, non-inferiority studies are relevant and necessary to support development and approvals of new antibiotics.