

FEATURE



ANTIBIOTICS

Speeding new antibiotics to market: a fake fix?

Antibiotic development may finally be picking up pace, with 11 new drugs approved in the past decade, four in 2014 alone, with the help of new legislation. But in this first installment of a series on antibiotics, **Peter Doshi** asks why authorities are approving drugs with little evidence they do anything to tackle the problem of antimicrobial resistance

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US president Barack Obama has called the problem of antimicrobial resistance “a serious threat to public health and the economy.”¹ In the UK, Sally Davies, chief medical officer for England, declared the problem “as important as global warming,”² and a “ticking time-bomb”³ while the prime minister, David Cameron, says: “we are in danger of going back to the dark ages of medicine.”⁴

Over the past few decades industry has turned its eyes towards the more profitable markets in chronic diseases—the blockbuster cardiovascular and psychiatric drugs, for example—and attention on much needed antibiotics has waned. This has resulted in fewer antibiotics able to keep up with the march of evolutionary resistance. Incentives for drug development have therefore become a key focus of efforts to tackle antimicrobial resistance, alongside improved infection control and antibiotic stewardship.

The Food and Drug Administration now offers a series of marketing incentives for new antibiotics. Backed by a law passed by Congress in 2012, 61 chemical entities have been granted “qualified infectious disease product” (QIDP) status, promising manufacturers accelerated review of new drug applications and five additional years of marketing exclusivity. Another bill introduced into the US Congress this year aims to substantially lower the requirements for FDA approval for certain new antibiotics, including the need for phase III trials, by allowing preclinical and pharmacokinetic data to serve as “confirmatory evidence” underpinning approval.⁵

So are the antibiotics approved under this new relaxed regime fulfilling the vision to treat infections that were previously untreatable because of resistant organisms?

Rising tide of new antibiotics—but are they better?

Four QIDPs were approved in 2014—dalbavancin, tedizolid, oritavancin, and ceftolozane/tazobactam, and a fifth, ceftazidime-avibactam, was approved in February. They promise to be the first of many.

The 2012 legislation that made this fast tracking possible—the Generating Antibiotic Incentives Now Act (GAIN)—says that to qualify as a QIDP, the antibiotics need to treat “serious or life-threatening infections, including those caused by an antibacterial or antifungal resistant pathogen.” Once granted, QIDP designation helps speed drug approval by placing the drug in either the “fast track” or the “priority review” regulatory pathway.

Ordinarily, drugs qualify for fast track when, in the FDA’s words, “data demonstrate the potential [of the drug] to address an unmet medical need.”⁶ Curiously, however, three of the five new antibiotics were approved to treat the same indication—acute bacterial skin and skin structure infections. Over 30 other drugs are already approved for these infections, of which at least six are approved for methicillin resistant *Staphylococcus aureus* (MRSA).

“There are no criteria requiring these products [dalbavancin, tedizolid, and oritavancin] to address an unmet medical need,” FDA spokesperson Stephanie Yao said in an interview.

Yet when I asked the FDA why new options for acute skin infections were important given the many existing approved therapies, the agency invoked the concept of unmet medical need: “New antibacterial drugs are critically needed to address current unmet medical needs and to ensure availability of antibacterial drug options to treat patients in the future.”

According to the FDA, a drug which both “treats a serious condition” and also, “if approved would provide a significant improvement in safety or effectiveness” qualifies for the other expedited approval mechanism, priority review.⁶ All five newly approved antibiotics received it, but QIDP designated drugs need not meet traditional criteria to qualify.

“A QIDP product is an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections and does not have to show added benefit in terms of efficacy,” the FDA told *The BMJ*. The implication is that “improvement in safety or effectiveness” does not apply to QIDP antibiotics.

The leeway granted to QIDPs is hard to understand considering that the driver for new drugs is the inadequacy of existing drugs. If there is no added benefit, what makes the drugs worth approving? I asked FDA which of the QIDPs showed added benefits, such as improved safety, but it did not give a direct response.

Companies were quicker to point out the benefits of their drugs. The Medicines Company, which makes oritavancin, said that the drug's once only dosing is an important added benefit over the older drug vancomycin, which is typically administered daily.

Steve Gilman, chief scientific officer of Cubist Pharmaceuticals, which manufactures tedizolid, said his drug's once daily administration addressed one of the "needs expressed by treating physicians." In addition, he pointed to the drug's oral formulation "which could reduce the need for costly hospitalization."

But does this supposed improved convenience of the new drugs deal with the original problem of resistance? All three of the new antibiotics for acute skin infections were approved to treat infections caused by certain susceptible bacteria and were studied in patients for whom effective drugs already existed; none lacked suitable treatment or were infected with difficult to treat drug resistant Gram negative microorganisms. "The statute does not require that a drug with QIDP designation provide effective treatment against infections resistant to all available treatments," the FDA said in a written statement.

Still, both industry and the Infectious Diseases Society of America (IDSA) argue that the new drugs are tackling the problem of antimicrobial resistance, pointing to the fact that the drugs are approved to treat MRSA infections (box).

Regulatory bait and switch

If the drugs don't directly deal with antibiotic resistance, what about providing additional treatment options for "serious or life threatening infections," as defined in the QIDP regulations? None of the approved drugs were ever tested to evaluate whether they saved lives. I asked the FDA how it could consider a drug like dalbavancin a QIDP when over 99% of trial participants did not die. The FDA wrote back: "Note that the requirement is that the drug is meant to treat 'serious OR life-threatening infections' (emphasis added)," highlighting the statutory definition.

But even if not necessarily "life threatening," it is questionable whether all patients enrolled in the studies had "serious" infections. Up to a third of patients in the new antibiotic trials had skin abscesses, but in earlier placebo controlled trials of skin abscesses antibiotics showed no benefit over incision and drainage alone, and no patients in the placebo group died or were admitted to hospital.⁹⁻¹¹ The manufacturer of oritavancin told *The BMJ* that 40% of patients in its pivotal study were treated entirely as outpatients, raising similar questions about underlying disease severity.

Worse than what we already have?

If the drugs are not proved to save lives, what benefit do the trials underpinning their approval demonstrate? Easy questions like these are surprisingly difficult to answer, at least in plain English.

Although the FDA requires most new drugs to show superiority to a comparator (either active drug or placebo) in randomized trials, antibiotics are often approved on the basis of so-called

"non-inferiority" trials. Even when trial data indicate the drug may be less efficacious than its active comparator, the FDA can approve it provided that the confidence interval around the effect estimate does not cross a prespecified "non-inferiority margin." The margin is supposed to represent the maximum amount of decreased effectiveness that remains "clinically acceptable."¹²

Even though the term "non-inferiority" suggests a new drug has an equivalent effect to the comparator, FDA guidance documents call this a "misnomer."¹³ Demonstration of equivalence, the agency says, "can only be demonstrated by showing that the test drug is superior."

The margin in antibiotic trials is typically set at 10-15% decreased efficacy, with industry and academic groups arguing that the number should be even bigger in order to decrease the sample size of studies. Dalbavancin, for example, was considered "non-inferior" to its comparator, vancomycin, because the lower bounds of the confidence intervals around the effect estimate in its two pivotal trials were -4.6% and -7.4%, respectively, above the prespecified margin of 10%.

All four QIDPs approved in 2014 were assessed in non-inferiority trials. The most recent QIDP approval, of ceftazidime-avibactam, was based on two phase II trials, both of which lacked any formal statistical hypothesis for inferential testing.¹⁴ A complete report of a non-inferiority phase III trial was not reviewed by the FDA before approval.

Some also question the assumption that non-inferiority trials necessarily put additional effective treatment options on the market.

"I've thought about it; I've looked at it carefully. I'm a professor of law and bioethics, and I can't figure this one out," says Kevin Outterson, from Boston University. Outterson is troubled by the nearly exclusive use of non-inferiority trials for antibiotics and says that they leave important questions unanswered. "People are comparing these new drugs to old drugs, but we don't know for sure how effective the old drugs remain because their clinical trials are ancient," he says. "You're not getting a [new] drug as good as vancomycin in 1958, but vancomycin today, diminished by resistance." As a result, the true effectiveness of the new drugs being studied is unclear. "Maybe now they're all not very good."

Hazy logic of antibiotic development

While the FDA celebrates new drugs approved under the GAIN Act, there remains no evidence the drugs meet unmet medical need, address antimicrobial resistance, or are more effective than pre-existing antibiotics. Nevertheless, some US congressmen argue that industry needs further incentives, and in January Senators Orrin Hatch and Michael Bennet introduced a new bill into Congress, the Promise for Antibiotics and Therapeutics for Health (PATH) Act.⁵ In a press release, Hatch declared the act would "allow health experts to more easily develop new treatments for antibiotic-resistant bacteria, and make real progress in preventing a great number of illnesses and deaths in the United States."¹⁵

The bill proposes lowering the requirements for FDA approval of new antibiotics that target unmet medical needs in specific, limited populations of patients. Instead of requiring substantial evidence from adequate and well controlled studies, the act would allow the FDA to "rely on sufficient evidence, which may include traditional endpoints, alternate endpoints, or a combination of [the two], and, as appropriate small clinical data sets; and . . . may rely on supplemental data, including preclinical evidence, pharmacologic or pathophysiologic

Rethinking MRSA

The *BMJ* asked manufacturers of the 2014 QIDPs how their drugs address the problem of antimicrobial resistance. Both the Medicines Company and Cubist cited methicillin resistant *Staphylococcus aureus* (MRSA). According to the Medicines Company, "Oritavancin has potent activity in vitro against methicillin-resistant *Staphylococcus aureus* (MRSA), a pathogen considered to be a serious antimicrobial threat by the US Centers for Disease Control and Prevention." But it is unclear whether this presents any true advance.

MRSA in fact is the only type of resistant infection specifically mentioned on the FDA approved drug labels. While according to the CDC, MRSA "is among the highest of all antibiotic-resistant threats" and accounts for almost half of the CDC's estimate of annual deaths from antibiotic resistant infections, the CDC also says that "the number of serious [MRSA] infections is decreasing."⁷ CDC cites a 31% reduction in overall rates between 2005 and 2011 and says that success has been driven by the prevention of infections, specifically central line associated infections, rather than drug treatment.

Raising further doubts about the role of drugs in the MRSA problem, the CDC stated in its 2013 threat report on antimicrobial resistance—prior to any of the QIDP approvals—that "there are multiple effective antibiotics for treating infections."⁷ It is far from clear that solutions to the problem of MRSA infections lie with the development of new drugs.

What is more, the perception that MRSA is intrinsically more dangerous than its susceptible counterpart, methicillin susceptible *Staphylococcus aureus* (MSSA), may be wrong. In a recent observational study comparing the long term outcomes after MRSA and MSSA infection, investigators found that patients with MRSA bacteremia had far higher mortality.⁸ However after patient prognostic factors had been adjusted for, mortality among MRSA and MSSA groups was similar. "The study implies that patients with MRSA bacteraemia do have a worse outcome, and it is likely due to the poor prognostic patient factors," study authors Lai Kin Yaw, Owen Robinson, and Kwok Ming Ho told *The BMJ*. "It does suggest that MRSA may be inherently no more dangerous than MSSA infections if strategies are in place to optimize the treatment of the patients." The authors indicated that a lack of drugs was not the key problem. "We would agree with you that we do have effective antimicrobial agents for both MSSA and MRSA bacteraemia," they said. "MRSA bacteraemia was associated with high crude short and long term mortality, but the attributable effect purely due to antibiotic resistance alone was likely to be small if strategies were in place to optimize patient outcomes."⁹

evidence, nonclinical susceptibility, pharmacokinetic data, and other such confirmatory evidence." These types of evidence would previously have been considered hypothesis generating.

Some companies have already asked FDA to accept lower standards of evidence even without new legislation. At an FDA advisory committee meeting in December, Cerexa advocated approval of ceftazidime-avibactam for hospital acquired pneumonia without presenting any data from a patient with the disease.¹⁶

Proponents argue these changes are necessary to study rare but important pathogens. "Some of the most dangerous pathogens currently infect relatively small numbers of patients, making it difficult or impossible to populate traditional clinical trials," IDSA president, Barbara Murray, told Congress last year.¹⁷ "It is important to develop drugs to treat infections caused by these deadly pathogens before they infect larger numbers of people."

To compensate for the limited clinical data, the proposed law would require new drugs to carry a logo or other wording "to indicate that the drug has been approved for use only in a limited population and that the safety and efficacy of the drug has been demonstrated only with respect to such limited population." In addition, the FDA would be given 30 days to review promotional materials before their release. According to the Pew Charitable Trusts, which supported the bill, these measures "will help ensure that patients who can be treated with other antibiotics are not put at unnecessary risk and will also help preserve the effectiveness of these vital new medicines."¹⁸

But others, like Outterson, suggest the numbers do not add up. "How are the companies going to make any money on this?" he asks. "If they only sell the drug to 5000 people for the first couple of years—due to stewardship—there is not much money in there."

Outterson notes that American courts have increasingly ruled in favor of permitting off-label marketing, which runs counter to the spirit of PATH even though the bill states, "Nothing in this subsection shall be construed to restrict the prescribing of antibiotics or other products, including drugs approved under the limited population pathway, by health care professionals, or to limit the practice of health care."¹⁵

The "limited population" concept is an ambitious goal considering that most antibiotics are used empirically in broad groups of patients, some of whom do not even have infections. And PATH carries no requirement for limiting the use of the new drugs through diagnostic tests.

Nevertheless, limited use or not, the evidentiary standards set forth in PATH suggest that future patients will be offered drugs with very limited evidence of efficacy.

"The thought process seems to be the assumption of some unmeasured future benefits for patients, but unless the new drugs are reserved and not used resistance will develop to them over time as well, so they will not be effective when needed in the future," says former FDA officer John Powers. "Drugs have different effects in different types of patients, and patients with disease due to resistant pathogens are on average sicker, older, and have more comorbid diseases and more comediations. Evidence already shows that non-inferiority on 'alternative endpoints' in patients with disease due to susceptible pathogens does not mean superior outcomes on saving lives in patients with disease due to resistant pathogens."

PATH calls for automatically expanding the limited population pathway beyond antibiotics to "other therapeutic areas" beginning in October 2016.

The offices of Senator Hatch and Senator Bennet did not respond to multiple requests for comment.

Lifesaving drugs that may not save you

In 2013, the FDA approved the antibiotic telavancin for treating nosocomial pneumonia. "Today's approval demonstrates the FDA's commitment to making available new therapeutic options to treat serious diseases like HAPB/VABP [hospital-acquired and ventilator-associated bacterial pneumonia]," announced Edward Cox, the director of the Office of Antimicrobial Products.¹⁹

But despite the FDA's excitement about a new treatment "option" for serious disease, neither of the two phase III randomized trials underpinning approval were designed to record 28 day all cause mortality. Rather, the primary outcome was "test of cure," a commonly used outcome in trials of anti-infective agents. This concerned Scott Komo, the FDA statistician who reviewed the sponsor's marketing application. Komo noted that according to the trial data, several participants were deemed "cured" by trial investigators within days of—and in some instances, on the same day as—their death.²⁰

In an interview, telavancin's manufacturer, Theravance, placed responsibility on the FDA for the company's selection of "test of cure" as the primary outcome. "In our Phase 3 HAPB/VABP studies, clinical response at the Test-of-Cure (TOC) assessment

was established as the primary outcome based on guidance from FDA,” the company said.

Because Theravance had not reported 28 day mortality, the FDA asked the company to provide the data. What the regulator found resulted in a boxed warning on the drug’s label: an increased risk of death for patients with renal impairment.²¹

Telavancin is not alone. In 2010, five years after tigecycline was approved by the FDA on the basis of non-inferiority trials, the regulator announced that the drug increased the risk of death. A meta-analysis by researchers at the National Institutes of Health estimated a 0.7% absolute increased risk of death with the greatest numerical increase in death in a trial of patients with vancomycin resistant enterococci and MRSA.^{22 23}

Increased risk of death was also observed in the pivotal randomized trial of bedaquiline, the first FDA approved drug to treat multidrug resistant tuberculosis. In this trial, nine of 79 patients that received bedaquiline died compared with two of 81 in the control group—a significant difference according to the drug’s label.²⁴

Each one of these drugs was approved under the FDA’s “fast track” designation.

History’s forgotten lessons

Perhaps most perplexing in the debate over relaxing regulatory approval standards is that the FDA is apparently endorsing it. In his book *The Antibiotic Era* historian and physician Scott Podolsky, comments: “The irony, after all, is that FDA antibiotic regulations—indeed, new drug regulations more broadly—were first articulated in the 1960s in the very setting of perceived loose antibiotic evaluations. The LPAD [limited population antibacterial drug] approach certainly has its uses, but its supporters should be cognizant of why and how existing FDA regulations were constructed in the first place.”²⁵

History has a way of repeating itself, and on this round, all indications point to a new era of faster and lower drug approval standards.

Competing interests: I have read and understood BMJ policy on declaration of interests and declare I know and consider some of the people interviewed in this article as colleagues. I was a corecipient of a UK National Institute for Health Research grant (for the HTA Update and amalgamation of two Cochrane reviews of neuraminidase inhibitors). In addition, I received support from the European Respiratory Society for travel to give a talk at the society’s 2012 annual congress in Vienna. I also received a 2015 new investigator award from the American Association of Colleges of Pharmacy to fund a PhD student to work on research on how the potential harms of statins are conveyed in drug labeling and pharmacy leaflets.

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Tracking the threat

Despite much talk about the increasing threat of antimicrobial resistance, the evidence for it is unclear. For example, the FDA's Janet Woodcock, director of the Center for Drug Evaluation and Research, says, "It is virtually undisputed that we are facing a tremendous public health crisis because of the rise of serious antibacterial infections and the simultaneous decline in R&D in this area."²⁶ The IDSA likewise stated in a 2010 journal article that "Drug-resistant infections and related morbidity and mortality are on the rise in the United States and around the world."²⁷

The BMJ asked the IDSA for data to support the assertion of an increasing threat. "Unfortunately, we must tremendously improve surveillance and data collection on antibiotic resistant infections both in the US and domestically," the IDSA said in response. "In the meantime, CDC's Antibiotic Resistance Threats 2013 and WHO's Antimicrobial Resistance: Global Report on Surveillance 2014 provide some useful information," both of which were published after IDSA's claim.^{7 28}

But neither report provides the data, and a recent Global Burden of Disease study found decreased mortality from infections worldwide between 1990 and 2013.²⁹ In an interview, coauthors of the CDC's report, Jean Patel and Steve Solomon, explained that it was a "first attempt" to estimate the combined impact of the 18 most significant antibiotic resistance threats in the United States. In 2013, the CDC estimated that at least 23 000 deaths a year resulted from antimicrobial resistance. But there is no prior estimate to compare with so we cannot determine whether that represents an increase, decrease, or no change from the past. "We have committed in the report to publishing updates periodically, so that going forward over time people will be able to track this," explained Solomon, who directs the CDC's Office of Antimicrobial Resistance. Solomon said CDC plans to revise estimates every two to three years.