Speeding new antibiotics to market: a fake fix?

Antibiotic development may finally be picking up pace, with four new drugs approved in the US in 2014 alone in the wake of new legislation. But Peter Doshi asks why authorities are approving drugs with little evidence they do anything to tackle the problem of antimicrobial resistance.

Barack Obama, US president, 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 un treatable because of resistant organisms? If there is no added benefit, what makes the drugs worth approving?

Rising tide of new antibiotics—but are they?

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 meticillin resistant Staphylococcus aureus (MRSA).

All five newly approved antibiotics were approved using the priority review mechanism, which qualifies a drug if it both “treats a serious condition” and also, “if approved would provide a significant improvement in safety or effectiveness.”⁷ But, the FDA explained, “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.”

Yet, if there is no added benefit, what makes the drugs worth approving? I asked the 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, and Steve Gilman, chief scientific officer of Cubist Pharmaceuticals, which manufactures tedizolid, both said their drugs’ once only dosing is an important added benefit over the older drug vancomycin, which is typically administered daily.

Gilman also pointed to tedizolid’s oral formulation “which could reduce the need for costly hospitalization.”

But how does improved convenience of new drugs deal with the original problem of resistance. 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.

Yet, although MRSA “is among the highest of all antibiotic-resistant threats” according to the US Centers for Disease Control and Prevention the number of serious MRSA infections decreased by 31% between 2005 and 2011, and the CDC says that success has been driven...
by the prevention of infections, specifically central line associated infections, rather than drug treatment.

What is more, the perception that MRSA is intrinsically more dangerous than its susceptible counterpart, meticillin susceptible Staphylococcus aureus (MSSA), may be wrong. Lai Kin Yaw, Owen Robinson, and Kwok Ming Ho, authors of a recent observational study comparing the long term outcomes after MRSA and MSSA infection, told The BMJ that “MRSA may be inherently no more dangerous than MSSA infections if strategies are in place to optimize the treatment of the patients.”

**Regulatory bait and switch**

It is not clear that these drugs provide additional treatment options for serious or life threatening infections either. None of the approved drugs were ever tested to evaluate whether they saved lives. Over 99% of participants in dalbavancin trials, for example, did not die and it is not clear that they 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

If the drugs are not proved to save lives, what benefit do the trials underpinning their approval demonstrate? Although the FDA requires most new drugs to show superiority to a comparator (either active drug or placebo) in randomised 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 pre-specified “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 Equivalence, the agency says, “can only be demonstrated by showing that the test drug is superior.” 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

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

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**COMMENTARY**

**Will 20th century patient safeguards be reversed in the 21st century?**

Most physicians and patients assume that medications are proved safe and effective. This hasn’t always been the case. The US FDA was born out of a series of 20th century tragedies: contamination of vaccines at the turn of that century; dangerous substances found in commonly sold medicines in the 1900s; deaths of over 100 children and adults in 1937 from a sulfa drug dissolved in diethylene glycol (antifreeze); extensive birth defects caused by thalidomide in the early 1960s; and infertility and deaths caused by the Dalkon Shield intrauterine device in the 1970s. Those tragedies all inspired laws that strengthened the criteria used to allow medical products on the market.

Subsequently, the first effective challenge to the FDA’s growing authority came from an unlikely source: people with HIV/AIDS. In the 1980s, as people with AIDS faced certain death, they criticized the FDA’s drug approval process as too slow and unresponsive to their needs. AIDS activists pressed for expedited drug approval and making experimental therapies widely available, demonstrating at FDA headquarters, and speaking out to FDA officials, the media, and Congress. They were remarkably successful, helping shape FDA reforms, including pathways for accelerated drug approval and expanded access programs for experimental medicines.

AIDS activists quickly learnt, however, that speedier approval and wider access had risks as well as benefits. They had assumed that any drug would be better than nothing, and that new drugs would be better than old ones, so they were greatly disappointed when the first generation of antiretroviral agents were less effective than expected. In fact, research did not confirm long term clinical benefit of these medicines; conflicting trial results and inconclusive studies piled up in the early 1990s. The activists realised that access alone does not necessarily provide answers, which now were in short supply.2 Much of this debate, however, became moot after a new generation of AIDS drugs, protease inhibitors, were used in combination with the older medicines. These new combinations had transformative clinical benefits, with dramatic reductions in AIDS related morbidity and mortality, raising patients from their deathbeds in what was called the Lazarus effect.3

The arrival of the AIDS epidemic in the US coincided with conservative presidential leadership and a growing conservatism among Congressional Republicans. Together, they sought to limit the size of the federal government and the scope of its powers. Although they had far different politics, AIDS activists had helped grease the wheels for a deregulatory agenda at the FDA. Starting in the early 1990s, a series of initiatives supported by conservative think tanks and drug industry lobbyists sought to further weaken the FDA’s authority and mandate, often invoking the legacy of AIDS activists and the rights of patients. AIDS activists balked at the appropriation of their work for these purposes, and in another unexpected turn of events, now defended the agency. But this time their protests went unheeded.4

In the 1990s, Congress began to gradually erode the standards used for drug approval and the safeguards for patients: reducing the number of studies required to get new drugs on the market from at least two to one and reducing restrictions on...
“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,” said Kevin Outterson, from Boston University. He is troubled by the nearly exclusive use of non-inferiority trials for antibiotics and says that they leave important questions. “People are comparing these new drugs to old drugs, but we don’t know how effective the old drugs remain because their clinical trials are ancient.”

Hazy logic of antibiotic development

While the FDA celebrates new drugs approved under the GAIN Act, there remains no evidence the drugs cater for 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. The bill proposes lowering the requirements for FDA approval of new antibiotics that target unmet medical needs in specific, limited populations of patients. Some companies have already asked the 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 out presenting any data from a patient with the disease. 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.

History’s forgotten lessons

In his book, The Antibiotic Era, historian and physician Scott Podolsky, comments: “The irony, after all, is that FDA antibiotics 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 FDA regulations were constructed in the first place.”

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. Peter Doshi, associate editor, The BMJ, pdoshi@bmj.com

Cit this as: BMJ 2015;350:h1453

Patients need knowledge—answers about the drugs they put in their bodies—not just access

...consequences. The 21st Century Cures draft legislation released by Republicans on the House health committee in January 2015 is sweeping and would jettison the phase III testing requirements for new drugs and largely dismantle the key components of the drug approval process in place since the thalidomide tragedy. Unsurprisingly, its proponents say the reforms are needed to meet patients’ needs. But patients need knowledge—answers about the drugs they put in their bodies—not just access.

If passed, this bill and other 2015 legislative proposals will radically alter the nature of drug, device, and biologics approval in the US, roll back patient safeguards, and leave an FDA that looks more like the one made public.

Medical devices are subject to even weaker approval criteria, with only 1% of devices reviewed through a process that requires clinical trials. Most of the thousands of medical devices not subject to clinical trials every year do not even get “approved” by the FDA, but are rather “cleared” for market—90% of them within 90 days. Nevertheless, the FDA has responded to political pressure by proposing a new expedited pathway for devices.

Now, Congress is proposing new legislation to further speed the drug approval process while further weakening the standards for safety and efficacy. It’s a trade-off with potentially deadly

AIDS activists learnt that speedier approval had risks as well as benefits

...the advertising and promotion of medical products. Despite numerous changes in White House and Congressional leadership, the 21st century has seen a steady escalation of legislation chipping away at the FDA. In response to legislative and political pressure, the FDA has offered numerous concessions to industry and its lobbyists. It now offers four pathways to speed the approval process for many drugs and biologics as well as an easier approval pathway for drugs for orphan diseases (those affecting fewer than 200 000 patients in the US). The standards for most drugs approved through expedited pathways are clearly lower, with smaller and shorter term studies than are otherwise required. For example, in 2008, an average of about 100 patients were tested with new drugs that were approved through expedited pathways, compared with almost 600 for standard approvals. As a result, patients relied on drugs for which safety and effectiveness were not always confirmed when they were first on the market. Instead of requiring clear proof of safety or effectiveness before approval, most evidence is not required until afterwards. Sadly, “required” postmarketing studies are often delayed for years, and when problems are discovered, corrective action doesn’t happen swiftly. It takes on average 11 years after approval for the FDA to institute new black box warnings, rescind approval, or require new risk information or contraindications be made public.

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2015 AWARDS
FINALISTS

★ DIABETES
TEAM OF THE YEAR

★ DEMENTIA
TEAM OF THE YEAR
Better diabetes care calls for better engagement with patients and carers, shortlisted entries in this award category seem to agree. Nigel Hawkes presents the teams that are stepping up to the challenge.

### SOUTH ASIAN DIABETES EDUCATION

One group that has proved resistant to open discussion of medical issues is the South Asian community, says Kiran Patel, who chairs the South Asian Health Foundation. He traces this reluctance to the culture of the subcontinent, where to admit to health problems was to risk marital capital. “We’ve struggled with community engagement,” he admits.

The answer came in asking local communities to arrange meetings themselves, outside health premises and in halls, temples, and gurdwaras (Sikh places of worship). A total of 11 events were held and covered broad-brush discussions about diabetes, the services available, and self-management. “We also did some myth busting,” he says. “For example, there’s a belief that if you start taking insulin to control diabetes, you’re going to die within 12 months. We explained that you’re not.”

“We also did some myth busting,” he says. “For example, there’s a belief that if you start taking insulin to control diabetes, you’re going to die within 12 months. We explained that you’re not.”

Outcomes from the programme, funded by an educational grant from Novo Nordisk, are qualitative rather than quantitative, but Patel is pleased to have found a formula that works in reaching a community with a high diabetes risk but a reluctance to talk about it.

### DIABETES PSYCHOLOGICAL MEDICINE SERVICE

“That way you can draw them out, and try to break the hopelessness they feel. This is a group that everyone has given up on. Without this service they would simply have been thrown on the scrapheap.”

Some patients, says psychiatrist Amrit Sachar, are an even tougher challenge. The combination of diabetes with mental illness can produce patients so alienated that persuasion is in vain. “We knew that depression and anxiety are two to three times more common in patients with diabetes,” she says. “But there is a small group with more profound problems, such as personality disorder or interpersonal difficulties that are played out through their diabetes. They feel they are being constantly criticised and punished. They’re a tiny group, but they take up a lot of healthcare.”

An opportunity to change this came with the ambitious integrated care scheme that has been developed in west London and includes Sachar’s trust, West London Mental Health Trust. This led to the creation of multidisciplinary teams that included a psychiatrist. “The effect was fascinating,” she says. “At the first meeting you would have a GP saying to a diabetologist that this or that patient had very poor control, and what else could he prescribe? Now they will often talk to the psychiatrist first. They’re realising that they have a lot of patients for whom another medicine isn’t an answer.”

She provides a different kind of psychiatric service, meeting patients in their homes or arranging to be introduced by a GP the patient trusts. “That way you can draw them out, and try to break the hopelessness they feel. This is a group that everyone has given up on. Without this service they would simply have been thrown on the scrapheap.”
"Patients are seen yearly, they’re tested, they come back and hear the results, then they’re reviewed again in six months. The scale of the decline is faster than the rate at which patients are seen”

“Diabetes care tends to be entirely reactive,” says Ian Gallen, consultant community diabetologist at Royal Berkshire Foundation Trust. “Patients are seen yearly, they’re tested, they come back and hear the results, then they’re reviewed again in six months. The scale of the decline is faster than the rate at which patients are seen.”

In west Berkshire four clinical commissioning groups collaborated to turn round results that in 2009-10 were among the worst in England. The approach included better education for patients and professionals, monthly team meetings, and virtual clinics supported by excellent IT. As community consultant Gallen spends the bulk of his time out and about, visiting the 52 general practices in the area to see patients identified by IT as being at particular risk.

“It works,” he says. Data show better control, with more patients completing care processes and more achieving glucose targets. There have also been savings of more than £800 000 a year in prescribing costs.

Type 1 diabetes in children and young people has its own set of problems. “It’s not just about compliance,” says May Ng, consultant paediatric endocrinologist at Southport and Ormskirk NHS Trust. “Clinics are faced with too few data—the vast majority of patients come in without sugar diaries. When they do bring them in, the diaries look superb but the numbers are fake. They just want to please you.”

“Clinics are faced with too few data—the vast majority of patients come in without sugar diaries. When they do bring them in, the diaries look superb but the numbers are fake. They just want to please you”

The answer was to combine the automatic uploading of insulin pump and glucose meter readings to a web-based system (DIASEND) with an information management system that all can access (Twinkle.net). That allows monthly audits to identify those with poor control, who are then visited at home by a member of the team. Facebook is also used for keeping in contact and providing advice when sought; “Almost 100% of 12 year olds use social media,” says Ng.

Control is improved, admissions are down, and so is length of stay. “Patients are very satisfied,” Ng says. The team achieved near maximum marks in the 2014 peer review assessment.

"The model of care was wrong—there was poor attendance at clinics and less than 20% were achieving an acceptable HbA1c of 59 mmol/mol”

NHS Tayside faced exactly the same problem. “There were poor levels of glucose control in children with type 1 diabetes,” says Vicky Alexander, consultant paediatrician.

“The model of care was wrong—there was poor attendance at clinics and less than 20% were achieving an acceptable HbA1c of 59 mmol/mol.”

“There is no single fix,” she says. The team implemented better training for children at key points in their lives, such as the transition from primary to secondary school. Monthly meetings are held by the team to monitor outcomes. And clinics are held outside the hospital, in a more social and relaxed setting in a building shared by social care and healthcare. “One thing they all say is that they want to meet other people in the same position,” she says.

Control has improved, with the proportion of new patients achieving an HbA1c of less than 48 mmol/mol rising from 12% to 48%. The proportion of established patients with HbA1c of more than 75 mmol/mol has fallen from 40% to 25%.
Dementia care today has a higher profile, helped by the government’s dementia strategy and driven by the enthusiasm of clinicians to seize the moment and make a difference.

Nigel Hawkes presents the shortlisted teams

**MEMORY CAFE**

At North Bristol NHS Trust a memory cafe has been established as a meeting point for carers. For two hours once a week they can share homemade cakes and tea and coffee with others in the same situation, often bringing the patients they look after along with them. Memory cafes are usually community assets, run by the Alzheimer’s Society, but to place one in an acute hospital is new and the society needed to be convinced it was a good idea.

Judy Haworth, specialty doctor in dementia care, says: “Both patients and carers need information and on the ward it’s often difficult to provide it. Junior staff don’t know what’s available. The cafe fills this need. While it’s true that an acute trust’s patients tend to be transient, it’s equally true that they’re often at a point of decision, an emotionally charged moment which makes information even more important. If carers are looking for a home for the person they care for, say, they can find out what they should be looking for.”

“Both patients and carers need information and on the ward it’s often difficult to provide it.”

**JUDY HAWORTH, SPECIALTY DOCTOR IN DEMENTIA CARE**

The cost is modest, the feedback good, and Haworth has been gratified that members of the hospital staff who are also in their spare time dementia carers are regular attenders. In a large hospital a small dementia team has been able to make a real difference for carers and for people with dementia, she says.

**DEMENTIA CHALLENGE PROJECT**

“The prime minister’s “dementia challenge” has a direct impact on a project in Surrey designed to identify patients with dementia, providing a grant of £250 000 to make it possible. Sen Kallumpuram, consultant psychiatrist at Surrey and Borders Partnership NHS Trust, explains. “Diagnosis rates in the Surrey Downs area were low. We did a search through the electronic records of 33 general practices, looking for patients diagnosed with cognitive impairment, Parkinson’s disease, heart diseases, diabetes, stroke, or transient ischaemic attack. We sent letters to 6500 patients and just under 2000 came for preliminary examination. Of these, 500 had a positive screening test, and half agreed after discussion to a referral to secondary services for more detailed tests. Of those who completed the tests, 85% were found to have cognitive impairment.”

“Of those who completed more detailed tests, 85% were found to have cognitive impairment.”

**SEN KALLUMPURAM, CONSULTANT PSYCHIATRIST**

The Dementia Team of the Year award is sponsored by Dementia UK. The awards ceremony takes place on 6 May at the Park Plaza, Westminster Bridge, London. To find out more go to thebmjawards.com

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Cite this as: BMJ 2015;30:h1553
Keeping patients with dementia out of hospital and in their own homes or care homes was the focus of the shortlisted project at Dorset Healthcare University Foundation Trust. Claire Simpson, consultant psychiatrist, says that patients often had to be admitted if they were acutely unwell, though a review in 2012 showed that 38% of inpatients could potentially have been treated at home. This was made possible by creating a “virtual ward” into which they could be notionally admitted, and sending out to treat them the same care team that would have cared for them as inpatients.

“Since we began, two thirds of patients have stayed where they want to be,” she says. “Patient and carer satisfaction has improved, and costs have been reduced.” The saving is considerable, around £500 000 a year.

Similar motivations inspired the team at Hertfordshire Partnership University NHS Foundation Trust, where a dementia course was established for family carers, particularly those faced with challenging behaviour from those they care for. Arun Jha, consultant old age psychiatrist at the trust, says that, in the past, clinicians have seldom been involved in helping carers and it was a gap that needed filling.

The answer was a “dementia first aid” course aimed at providing basic knowledge to carers, initially 12 hours over two days but reduced to one four-hour session plus web-based support after feedback from participants. The course includes training in mindfulness, retained in the reduced format because people enjoy it and it helps them deal with stress. “They discover that they’re not alone, and that different people cope differently with problems, so they learn from one another,” Jha says.

“We are doing a long term study to see if training family carers reduces or delays hospital admissions. If carers are trained and know what to do, it would have that effect.”

Raising the quality of care in residential homes is demanding, admits David Somerfield of Devon Partnership NHS Trust. A TV documentary by business expert Gerry Robinson in 2009 had shown that South Devon had some of the best and some of the worst dementia care homes. “That galvanised us, but we couldn’t get the funding at the time,” he says. The prime minister’s “dementia challenge” fund came to the rescue with a two year grant worth £255 000.

“As soon as you have trained one lot of staff, they’re gone. So we got together with care home owners and tried to identify people who would be around a while.”

David Somerfield, Medical Director and Consultant Psychiatrist

“One problem is that as soon as you have trained one lot of staff, they’re gone. So we got together with care home owners and tried to identify people who would be around a while. With 180 care homes in South Devon and the attainment standards of staff generally low, you can’t hope to do it all at once. We focused on 13 homes and used another 10 as controls.”

The project identified dementia “champions” in each home, working with them to improve knowledge, leadership skills, and confidence. Other staff were also trained, though less intensively. The aims were to improve care in the homes and reduce emergency admissions. The first appears to have been achieved, with good feedback from patients and carers; the second will be the subject of longer term analysis, conducted independently by a team at Plymouth University.
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