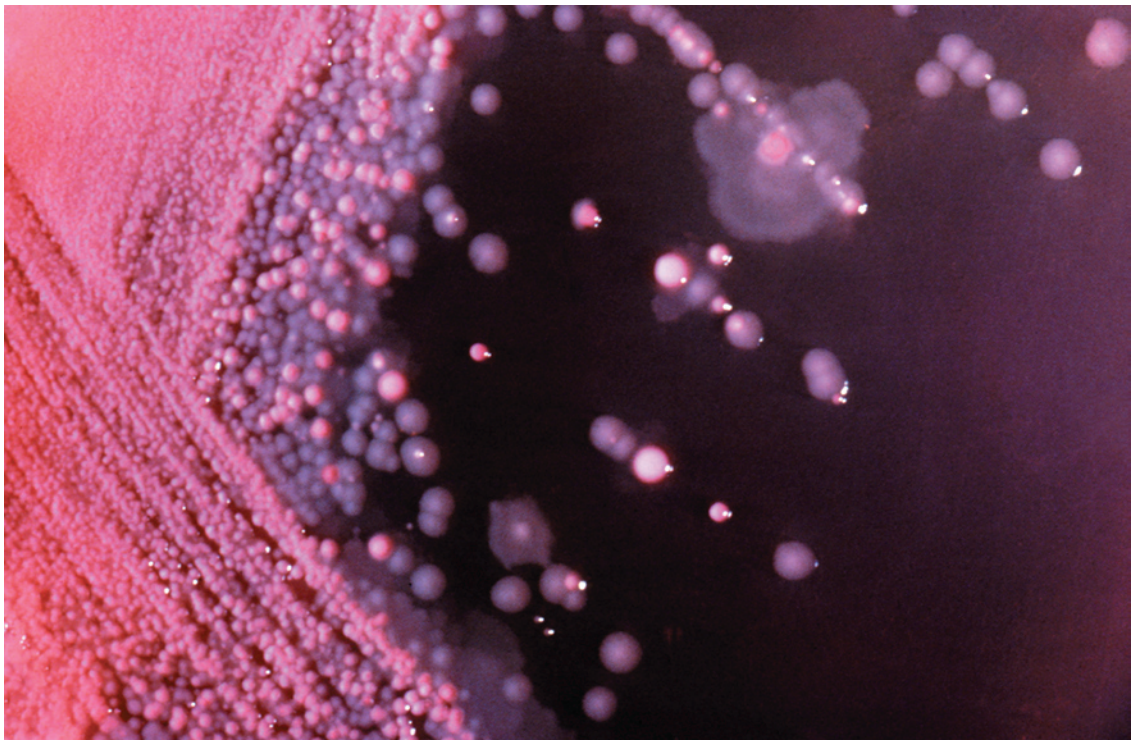

CDC/DR GILDA JONES

Bad bugs need more drugs

Dramatic increases in the prevalence of multidrug-resistant bacteria have put the spotlight on the lack of new antibacterials coming through the pipeline. How might regulatory guidance for clinical trials of antibacterials help tackle this shortfall?

Alisa Opar

The US FDA in October issued the first of its long-awaited guidelines for clinical trials of drugs to treat bacterial infections. Prompted by the Infectious Diseases Society of America (IDSA), the requirement to issue guidance was part of the FDA Prescription Drug User Fee Act (PDUFA IV), reauthorized in September, which contains provisions aimed at promoting and strengthening the antibacterial pipeline.

Novel agents are needed to combat the dramatic increase of antibacterial-resistant community and hospital-acquired infections. For example, England and Wales have seen the number of deaths due to Methicillin-resistant *Staphylococcus aureus* (MRSA) jump from 51 in 1993 to 1,629 in 2005. In the US, the infection killed nearly 19,000 people in 2005. Other antibiotic-resistant bacteria are evolving and the existing arsenal of drugs is increasingly powerless against them.

"While we certainly do need to work on hand-washing and efforts to slow the spread of drug-resistant infections, we're going to need new antibiotics to treat bacteria that are resistant to the antibiotics that we have," says Brad Spellberg, an infectious disease researcher at the University of California, Los Angeles, USA. "There's no way to get around that."

At the same time, the pipeline has nearly dried up. According to Stuart Levy, a microbiologist at Tufts University, USA: "It's lean, unbelievably lean, especially for drugs to treat the really hardcore, multidrug resistant organisms like *Pseudomonas* and *Acinetobacter*." In the past decade, the FDA has approved ~10 new drugs, only two of which have novel mechanisms of action. Fourteen drugs are in development — a sharp drop from the dozens in the works 25 years ago.

One PDUFA IV amendment aimed at improving the development pathway for new antibacterial agents stipulates that, within 1 year, the agency must issue guidance for the conduct of clinical trials for

antibiotic drugs. The first draft guidance covers trials for acute bacterial sinusitis (ABS); the agency plans to release guidelines for acute bacterial otitis media, acute bacterial exacerbation of chronic bronchitis and others within the time frame.

Historically, the FDA has required non-inferiority trials, in which a new antibacterial must prove to be no worse than existing drugs. The new guidance documents indicate that non-inferiority trial designs are not appropriate for many kinds of antibacterials, and placebo-controlled studies should be used instead. With ABS, for instance, patients typically get better with or without antibiotics, so it can be difficult to tell whether a drug is efficacious. But non-inferiority trials are sometimes necessary. "For more serious infections, placebo-controlled trials are not an option, so non-inferiority studies remain an appropriate study design," says Edward Cox of the FDA.

IDSA is "pleased that the FDA has issued the long-delayed" ABS guidelines, says public policy director Robert Guidos, adding that the group has not yet had time to review them.

"The more information that the FDA can provide to the drug development people, the better, because the industry, not infrequently, is guessing as to what sort of trials it will take to get an approved indication," says Barry Eisenstein, Senior Vice President of Scientific Affairs at Cubist Pharmaceuticals.

Yet others say the new guidelines might raise the bar too high. "I think it's actually going to make it difficult for companies to complete bacterial sinusitis studies," says Spellberg.

Levy agrees. "It's going to cost more money because it's going to involve more patients. It's going to deter companies, at least for those indications in the community, not in hospitals."

All infectious disease trials have challenges: finding enough participants to enrol in studies on less frequently occurring diseases; balancing the urgent need to begin therapy with determining eligibility; and figuring out whether a person actually has the disease being studied. "At the time that you're actually enrolling the patient, you might not know if they have a bacterial cause of their disease," Cox says.

Better diagnostic tests could help get those answers more quickly. Small biotechs and some international groups, such as TheraEDGE, a consortium of European partners from industry and academic institutions, are at the forefront of developing the technology. In January, TheraEDGE is launching a project to develop a molecular diagnostics device to detect and identify organisms causing community-acquired lower respiratory tract infections in 20 minutes; current analysis can take days, according to project coordinator Jordi Carrera, biomedical area manager of NTE (Barcelona).

> "We have to be creative in getting big industry back in the game"

Better clinical trial design and diagnostics are steps in the right direction, but experts say major drug companies need to resume making antibiotics to make real headway. In recent years, former pioneers such as Eli Lilly and Aventis have left the field. While smaller companies might identify promising candidates on their own, they often need the resources of big pharma to move agents into clinical trials and the market. "We have to be creative in getting big industry back in the game," says Levy. "Although small biopharmaceutical companies are filling the void."

IDSA has put forth several suggestions, including liability protection, patent extension and advanced purchase commitments from the government. In September, Congress raised the authorization level of Orphan Drug grants and contracts from US$25 million to $30 million. Although the funds haven't been designated, IDSA hopes they will flow into antibiotic development.

Biotech and pharma companies with active antibacterial programmes are changing their focus to try to generate more candidates. In the mid-1990s, many turned to high-throughput screening of compound libraries to find targets for novel antibacterials. They identified some, but the approach wasn't successful, according to Karen Bush, a microbiologist at Johnson & Johnson. "The industry doesn't have anything in a clinical trial that has gone beyond a Phase I study for any of these new targets. It's been very disappointing, demoralizing," she says. As a result, some companies have walked away from high-throughput screening, and instead are returning to more traditional approaches.

Among those evaluating natural products, Cubist has collected samples from all over the globe. But, as Eisenstein points out, natural-products screening is labour intensive, and "it could be the case that most of the low-hanging fruit has been plucked."

Cubist and other companies are also revisiting older compounds, looking for new ways to overcome resistance. For instance, Tygacil (tigecycline; Wyeth) — the first member of the glycylcycline class and a semi-synthetic derivative of a tetracycline — is effective against tetracycline-resistant Gram-positive and Gram-negative pathogens. Both Cerexa and Johnson & Johnson have Phase III, broad-spectrum cephalosporin antibiotics with anti-MRSA activity. "My guess is that we will see more new drugs coming from the old classes than we will see new targets and novel mechanisms," says Bush.

Companies are pursuing less conventional approaches too. Mutabilis and Paratek are working on small-molecule inhibitors that disable bacterial virulence in Gram-negative and Gram-positive pathogens. And Novozymes is developing antibacterial peptides for use against pneumonia and other diseases.

These myriad efforts are critical in the race against ever-adaptable bacteria, says Eisenstein. "Even if new drugs are used optimally, there will always be selection for resistance. Over time, the resistance builds up until you've evolved the bacterial targets to the point that you can't use those drugs any more."