Antibiotic bill doesn't GAIN enough ground

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With an eye to tackling the growing problem of antimicrobial drug resistance, US lawmakers last month proposed new incentives to jump-start the ailing antibiotic industry. But the legislation as written is not likely to have the intended consequences, as it fails to adequately shield companies from competition with generic drugs. To truly entice investment and research from the drug industry, the bill needs to simplify the path to regulatory approval, provide greater protection from generic competition and aid drug companies with intellectual property extensions, tax relief and guaranteed market commitments.

The prevalence of hospital-acquired superbugs has reached an all-time high, claiming the lives of as many as 70,000 people per year. Yet, at the same time, drug development for new antimicrobial agents is at a historic low point. Recognizing the health risk posed by this disconnect, the World Health Organization and the Infectious Diseases Society of America unveiled separate strategic plans in April calling for increased surveillance of antibiotic-resistant microbes, more responsible use of existing antimicrobial medicines and incentives to create new drugs. But even with these calls to action, drug companies have been reluctant to make the large investments needed into antibiotic research and development (R&D) because of the high risk and low return compared to drugs for other diseases.

In an effort to change the R&D calculus, on 15 June lawmakers led by US representative Phil Gingrey, a Georgia Republican and a physician, reintroduced legislation called the Generating Antibiotic Incentives Now (GAIN) Act. The bill, which failed to pass when it was first proposed in September 2010, aims to grant speedier application reviews from the US Food and Drug Administration (FDA) for certain experimental treatments against infectious disease, and, if the drugs are licensed, extend marketing exclusivity by an additional five years (on top of the existing five). Together, these provisions ultimately result in more time for the drugmaker to benefit from its R&D investment.

Although the GAIN Act is a good first step to encouraging the development of new antimicrobial drugs, the bill's current provisions won't be enough to attract big pharma investment, nor will it assist smaller and more productive biotech companies that are often venture capital funded. The writing is already on the wall that the drug industry hasn't been swayed by the proposed legislation. In February, for example, the largest pharmaceutical company in the world, New York–based Pfizer, announced that it was shuttering its antibacterial drug development unit in the US, even though the drugmaker knew that the GAIN Act was close to reintroduction and probable approval. Then, in April, a subsidiary of New Jersey's Johnson & Johnson—the world's number-two pharma firm—also decided to drop its antibiotic program.

The GAIN Act is not enough, because the payback for the pharmaceutical company is a long way off, and a lot can happen in the 15-year interval from discovery to market approval—resistance, competing new drugs, dramatic changes in the market place or legislative arena, and so forth. The priority review granted in the GAIN Act means only an early initial FDA answer regarding the drug's chances for approval—rather than an increased probability of approval. GAIN Act or not, most important new antibiotics are going to receive priority review, as happened recently with Optimer Pharmaceuticals' *Clostridium difficile* drug Dificid (fidaxomicin), which won regulatory approval in May (see page 762).

Indeed, the legislation will not have the intended impact unless the current regulatory landscape changes in two major ways. First, the juice from medical reimbursement for a course of antimicrobials needs to be worth the squeeze for antibiotic development. Even though new antibiotics can have huge health benefits for society, as long as the price—and, therefore, profit margins—for these medicines remain low, pharmaceutical companies will probably never bother throwing money behind antibacterial R&D. Why should they, when lifestyle drugs, such as those for male pattern baldness or erectile dysfunction, or treatments for chronic illnesses are taken for many years at considerable costs, and, as such, provide significantly more return on investment? The reality is that even though antibiotics can add decades to the life of a 25-year-old with a deadly superbug infection for less than $1,500, the market conditions cause most drugmakers to develop $100,000 cancer drugs, for example, that typically extend the life of a senior citizen by just a few months to several years.

A second necessary change to the landscape is a realignment of FDA expectations of clinical trials designed to test new antibiotics. The current flawed procedures do not reflect real-world scenarios and fail to provide a clear regulatory path to approval. For example, in the name of statistical purity, the 2009 guidance for developing treatments for hospital-acquired or ventilator-associated pneumonia calls for study subjects who have not received antimicrobial therapy within 30 days of enrollment. This is an onerous prerequisite: essentially all patients with ventilator-associated pneumonia who are infected with drug-resistant pathogens (which is why new drugs are being developed in the first place) will have received prior antimicrobial therapy. What's more, the guidance document recommended by the FDA relies on all-cause mortality as the clinical endpoint, which is a highly confounded outcome measure and is poorly related to drug exposure (greater than 50% of ventilator-associated pneumonia–related deaths are unrelated to antibiotic exposure) in determining the success of drugs directed against infectious agents.

In addition to the GAIN Act's provisions, legislators should introduce R&D tax credits, research subsidies and, most importantly, guaranteed market commitments and longer marketing exclusivity (longer than ten years from approval) to boost the ailing industry. Furthermore, drug companies should be offered tax relief for educational programs that promote the appropriate use of antibiotics. Such measures could ultimately benefit both industry and society at large.

Certainly, the antibiotic industry has undergone deterioration. With a few notable exceptions, such as AstraZeneca and GlaxoSmithKline (both, interestingly, UK-based companies), big pharmaceutical firms across Europe and the US have largely abandoned antibacterial R&D, relegating antibiotic innovation to only small biotechs companies. The industry needs companies of all sizes in the antibacterial game, as the risks posed by antibiotic-resistant bacteria are a grave threat to public health. And, to tackle that, the industry needs a variety of investment incentives to move the ball forward. The current situation—a dichotomy of squeezing down antibiotic prices while, at the same time, disincentivizing the industry—does not benefit anyone. Clearly, pricing of antibiotics needs to be commensurate with their societal value if we are to meet the challenge posed by superbugs and avoid a public health disaster. The GAIN Act is a good first step, but it is far from enough.

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