NEWS IN BRIEF

FDA dissects 12 years of complete response letters

A review of 151 drug application rejection letters unveils the most common and problematic efficacy and safety deficiencies in new drug submissions.

The lowdown: Complete response letters — in which US drug regulators lay out their reasons for rejecting drug applications — are bad news for drug developers. But some letters are worse than others. To get a grasp on the types of issues that sink submissions, and the implications of the different problems, the FDA has now released a retrospective review of complete response letters to 151 rejected regulatory applications for new molecular entities (NMEs) issued between 2000 and 2012 (*JAMA* **311**, 378–384; 2014). Safety issues are easier to overcome on resubmission than are efficacy issues, the agency concludes.

In their heuristic analysis, Leonard Sacks, of the FDA, and his colleagues first classified complete response letters depending on whether they flagged up efficacy deficiencies (32%), safety deficiencies (26%), efficacy and safety deficiencies (27%), or chemistry, manufacturing and controls (CMC) and/or labelling problems (15%). Of the efficacy deficiencies, the most common problem was poor dose selection, which the authors note can be avoided with adaptive trial designs or other dose optimization strategies. Poor end point selection and inconsistent results when multiple end points were used also made up a large proportion of the efficacy deficiencies. On the safety side, clinically observed adverse events were the most likely to preclude a first-round approval. Theoretical risks related to drug mechanisms of action, structure or class were noted in 7% of first-round complete response letters.

Of 151 NMEs that received first-round complete response letters, 87 were resubmitted during the study's timeline. Of these, 71 were eventually approved (78% were approved on their second review, 18% after their third review and 4% after further rounds of review). But whereas 62% of resubmitted drugs with safety concerns alone were subsequently approved, only 31% of resubmitted drugs with efficacy concerns alone ever got an eventual green light. This discrepancy could be because safety problems can be addressed by appropriate labelling and risk management strategies, the authors note. Of 11 drugs that were rejected on their first review owing to increased overall mortality, none was approved upon resubmission.

"Our findings suggest areas of deficiencies in new drug applications in which strategies for drug development could be improved," the authors write.

An antibiotic comeback?

After years of industry-wide disinvestment from antibiotic research, a few large companies are re-investing.

The lowdown: In 1999, Roche was one of the first large pharmaceutical companies to pull out of antibiotic research. Bristol-Myers Squibb, Lilly, Abbott, Bayer and others followed, and Pfizer closed its main antibiotic research centre as recently as 2011. But now, with the threat of antibiotic-resistant bacteria growing, a turnaround may be underway.

Late last year, Roche partnered with Polyphor to re-enter the antibiotic space, paying up to US$550 million biodollars to collaborate on the development of the Phase II macrocyclic peptidomimetic POL7080 for *Pseudomonas aeruginosa* infections. In January, AstraZeneca and Sanofi made antibiotic investments of their own. AstraZeneca, one of the few companies that has maintained a presence in this area over the past decade, partnered with FOB Synthesis to combine a β-lactamase inhibitor with carbapenem antibiotics. And Sanofi, which spun out its antibiotic research in 2004 but has been re-establishing its interest in the area since 2011, partnered with Fraunhofer-Gesellschaft to identify and optimize novel naturally occurring chemical and biological anti-infective compounds.

"We think it is the right time to get back in," says John Reed, Head of Pharma Research & Early Development (pRED) at Roche. Advances in clinical trial design, diagnostics and target space have made antibiotic research more appealing now than it was a decade ago, he told *Nature Reviews Drug Discovery* (see page 170).

Many antibacterial experts, however, remain concerned that the commercial incentives don't yet outweigh the challenges of antibiotic development. Although the GAIN (Generating Antibiotic Incentives Now) Act was enacted in the United States in 2012 to shift the balance (for instance, with 5 additional years of market exclusivity for antibiotics), a bipartisan group of representatives introduced the ADAPT (Antibiotic Development to Advance Patient Treatment) bill to the US House of Representatives in December to, among other things, create an accelerated approval pathway specifically for antibiotics.

The BACE race is on

Merck and AstraZeneca are advancing their BACE inhibitor into pivotal trials, leaving Lilly behind.

The lowdown: Under the amyloid hypothesis of Alzheimer's disease, the amyloid precursor protein is cleaved by β-secretase (BACE) and then by γ-secretase to release amyloid-β, which forms the plaques that may be responsible for neurodegeneration. So far, however, amyloid-targeting antibodies and γ-secretase inhibitors have failed in Phase III trials to affect disease symptoms or progression. BACE inhibitors are now stepping up to the pivotal trial plate.

Merck and Co. are in the lead, since initiating in November a Phase III trial testing MK-8931 in 1,500 patients with amnestic mild cognitive impairment due to Alzheimer's disease (prodromal Alzheimer's disease). A Phase II/III trial is also underway, testing the drug in 1,960 patients with more advanced mild to moderate Alzheimer's disease. AstraZeneca is in close pursuit, announcing in February that it will advance its Phase I candidate AZD3293 into a pivotal Phase II/III trial this year. It has not yet disclosed trial design details.

But while Merck and AstraZeneca speed ahead, Lilly has put the brakes on its BACE inhibitor LY2886721. In January Lilly stopped a Phase II trial of the drug after observing abnormal liver biochemical tests. Lilly does not think that this toxicity was a class effect, and says it is still interested in developing BACE inhibitors.