FDA Analysis of Antibiotic Development - with Hubris!

July 1, 2020 by David Shlaes

(This post originally appeared on David Shlaes's personal blog)

The US FDA just published an analysis of antibiotic development looking back over the last 40 years. The paper was accompanied by an editorial by Rex and Outterson. These papers are well worth reading and I highly recommend them for everyone whether they are familiar with antibiotic development or not. I must say that the hubris of the FDA analysis is astounding (see below).

The FDA paper documents and quantifies a number of facts most of us already know.

- Antibiotic discovery and development as gone from predominantly large pharma to almost all biotech.
- The number of approvals of new antibiotics has drastically decreased in the last two decades (with a modest increase in recent years).
- The success in achieving market approval plummeted by 50%.

Two observations that were of high interest were that clinical development times have increased substantially and that the antibiotic classes being developed have changed to large percentage of classes outside of B-lactams, macrolides and quinolones. The FDA notes that there has been a recent increase in the number of B-lactamase inhibitors in development (a welcome change as far as I'm concerned), as well as an increase in "others." I think that this may be related to the biotech nature of sponsors and their willingness to pursue non-traditional avenues such as peptides, peptidomimetics, new targets, etc. This also may help explain the lower success rates since, by definition, these may be higher risk ventures.

Figure 1

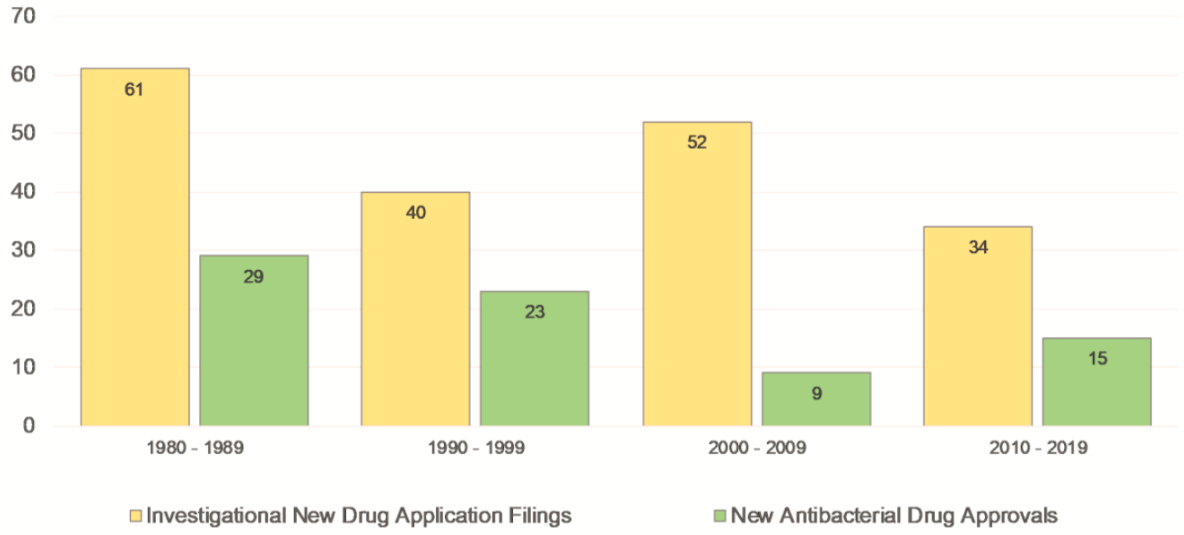
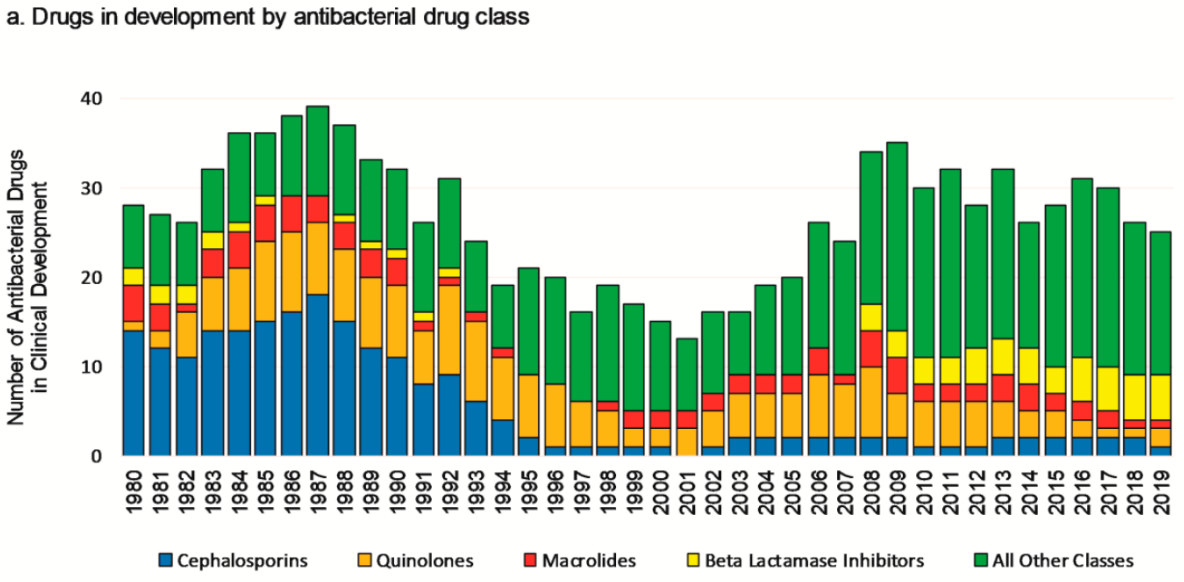


Figure 2



The prolonged development times may also be partly explained by the change to biotechs where discontinuation of development may not be reported to the FDA in a timely way. But – a KEY reason for the decreased success rates and prolonged development times lies with the FDA ITSELF. This fact is

conveniently ignored both by the FDA authors and by the accompanying editorial. Let us remember that in 1999-2000 the FDA began to tighten their antibiotic trial design requirements that led to increase development costs and timelines. This was, in fact, one of the several factors that led to the abandonment of antibacterial discovery and development by large pharma starting in 1999. Then came the Ketek scandal of 2006 where the FDA yielded to congressional pressure and essentially brought antibiotic development to a virtual halt (with just a few exceptions). They finally realized their mistake and the resulting disaster for antibiotic developers and reversed course in 2012. But this resulted in extensive damage to the industry and our pipeline. For a complete review of this history – see my book – Antibiotics – the Perfect Storm published in 2010.

The FDA notes that today only 8 of 25 drugs in development target critical multiply-resistant Gram-negative pathogens. They note the increase in development of drugs on novel classes, but they also not the higher risk associated with such compounds. They wonder if failure of a program using a novel class would doom the entire class. That is a good question and I suspect the answer will have to be provided on a case by case basis.

The FDA also questions whether the prolonged development times translate into higher development costs. That may be true. But the FDA does not consider the incredible cost associate with the post-approval obligations that occur if a drug should make it all the way. This is a topic covered by the accompanying editorial.

Clearly, the FDA analysis confirms what we already know about the fragility of our antibiotic pipeline. The increased development time, higher risk of failure, increased costs, and burdensome post-approval obligations all work to discourage scientists, entrepreneurs, investors and companies from entering or continuing in the antibiotic space. The paucity of our pipeline therefore is not surprising.

As the editorial by Rex and Outterson points out, without significant pull incentives to address market attractiveness we will be doomed to a failing pipeline for the forseeable future.