Antibiotics – The Last Frontier

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In 2010 my book, "Antibiotics – The Perfect Storm" was published.[1] (I use the term antibiotics to include any small molecule antibacterial drug). At that time there was (and still is today) an increasing frequency of bacterial resistance to even our antibiotics of "last resort." The perfect storm consisted of a number of converging pressures on our ability to maintain any kind of reasonable pipeline of new antibiotics in the face of this public health threat as shown in Box 1.

As a result of this "perfect storm", our antibiotic pipeline is dangerously thin as demonstrated by a recent report from the World Health Organization.[2]

Some things are looking brighter today. We are making slow but important progress in our scientific understanding of antibacterial drug discovery especially for those difficult to target gram-negative pathogens.[3]

BOX 1

Antibiotics – The Perfect Storm (2010)[1]

- Bacteria are becoming resistant to antibiotics faster than we can find new ones.
- Discovering new drugs is hard.
- The FDA is living on another planet.
- The market for antibiotics is soft.
- Industry is consolidating faster than a speeding bullet.
- Companies continue to abandon antibiotics research.

The FDA[4] and the European Medicines Agency[5] have provided a number of streamlined clinical development pathways for antibiotics active against key resistant pathogens that will save time and money and will get those new products to patients and their physicians in a timelier manner. Encouraged by these developments, some pharmaceutical companies have restarted their antibiotic research efforts, although the total number of large companies engaged in the area has not really changed since 2010.[6]

The Biomedical Advanced Research and Development Authority of the Department of Health and Humans Services in the U.S. and the Innovative Medicines Initiative in Europe have been providing substantial financial support to companies trying to develop new antibiotics of high priority.[7] These "push" incentives reduce costs for any given product considerably – but this will not be enough.

We are beginning to make progress on training a new generation of antibiotic hunters. A collaboration between CARB-X* and GARDP** has begun to put together a series of workshops, lectures and webinars aimed at training researchers in key aspects of antibiotic discovery and development. The first series of workshops occurred at the 2017 ASM-ESCMID meeting in Boston and were called Antibiotic Bootcamps.[8] (They covered early discovery, manufacturing and microbiology). More are planned for the near future.

One area where we have made no progress is the economics of the antibiotic market. A summary of sales for recently approved antibiotics is shown in Table 1. These sales figures pale in comparison to drugs for cancer, psychiatric disease and cardiovascular disease.

One aspect of the market that people fail to understand is that

*CARB-X = A Boston-based international collaboration, *Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator*

**GARDP = *Global Antibiotic Research and Development Partnership*

Table 1. Sales of Recently Approved Antibiotics[12]

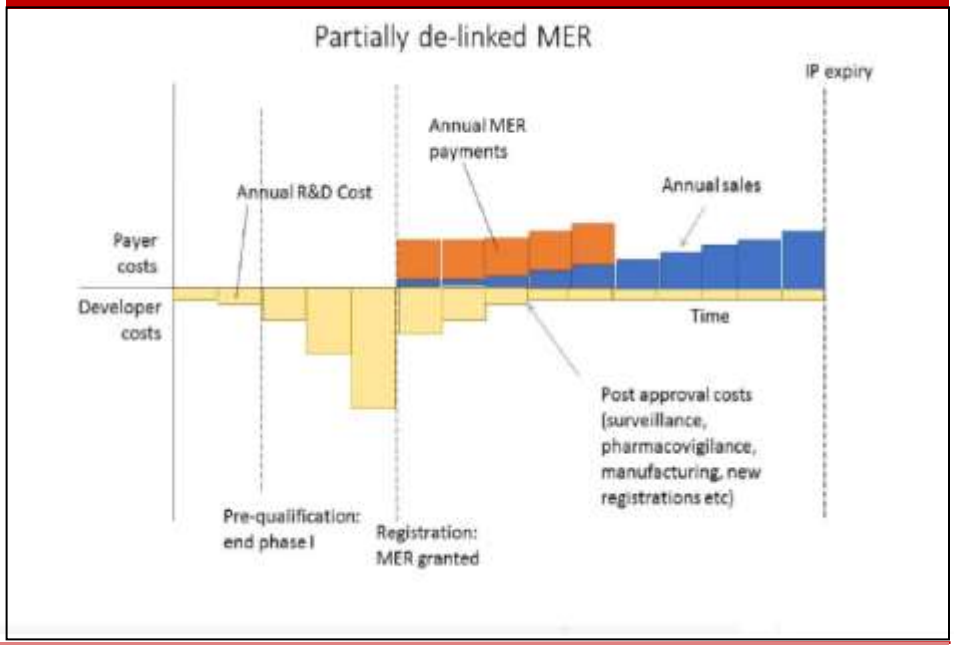
Antibiotic	Year of U.S. Regulatory Approval	2015 Sales (Millions USD)
Ceftazidime-avibactam	2015	35.8
Tedizolid	2014	37
Dalbavancin	2014	20.3
Oritavancin	2014	9.1
Fidamoxicin	2011	39.8
Ceftaroline	2010	118.5
Telavancin	2009	9.4

the major cost for a company is not directly related to the product in question. It is the cost of all the prior failures.[9] And, in the drug discovery and development world, failure is the general rule. Over 95% of compounds discovered in the laboratory will never make it into human trials. Of the small number that do enter clinical development, only 20% or so will actually be approved and enter the marketplace. It is the enormous cost of all these failures that make drug discovery and development such a high-risk endeavor. The most recent estimate of these costs for a single drug was $2.6 billion.[9] And it is these costs that any product making it all the way to the market must pay in addition to some profit for shareholders of these companies and to fund further research. Clearly, the antibiotic market is unable to provide these required returns on investment.

Over the last several years, a number of proposals have been presented to address the failed market for antibiotics.[10-12] They all come down to some sort of guaranteed payment at the time of market entry. One example of this was recently proposed by Drive-AB, a European project to propose solutions to the antimicrobial resistance problem (Figure 1).[13] As shown in this example, a market entry award would start paying a company at the time they received approval for their new antibiotic that had previously been designated a candidate for such an award based on medical need and priorities such as those proposed by the Centers for Disease Control in the U.S. or the WHO.[14,15] The continued availability of award payments would be contingent on the company meeting certain predetermined milestones around manufacturing, physician education, and other key elements. In this particular formulation, the company would also be allowed to charge some price for the antibiotic and this price might grow after the market entry reward payments ceased. Drive-AB has suggested, based on mathematical simulations, that such a market entry reward would ultimately quadruple the number of new antibiotics approvals.[13]

Several other market solutions have been proposed and discussed.[10-13, 15] One, for example, would provide a guaranteed purchase of a given product over time as a kind of insurance or, as some would say, something like fire extinguishers and fire departments.[16] We pay for them but hope never to use them. In another, we provide an exclusivity voucher such that the recipient is awarded an additional period of exclusivity for a product

Figure 1. One model for a Market Entry Reward (MER)[13]



of their choice from their portfolio.[12] This voucher could be kept or sold. Of course, its monetary benefit would have to be capped and the award would still be subject to contractual constraints, as would be true of all the market entry rewards being discussed.[12] All these proposals come down to a societal determination of the value of antibiotics in general and the particular product specifically. All also depend on government intervention to provide any payment regardless of the particular solution under discussion. The differences among all the proposals revolve around how the payments are funded by society. Does it come from general revenues spread out among all taxpayers—or does it come from only specific subpopulations of taxpayers?

There is no doubt that the antibiotic pipeline today is in dire straits.[2] Regardless of the incentive model one prefers, there is no question that unless we do something soon to address the failure of the antibiotic market, our pipeline of new antibiotics and our ability to deal with bacterial infections in the future will suffer further. We risk losing the miracle of antibiotics for our children and grandchildren. Lets invest today to prevent that unimaginable outcome.

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