



Antibiotic Development in a Time of Escalating Bacterial Resistance

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Received date: September 02, 2014, Accepted date: February 12, 2015, Published date: February 19, 2015

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Commentary

It is evident that few classes of drugs have made such a remarkable impact on human health as antibiotics. The marked drop in mortality, serious sequelae and overall benefit to society due to decreased morbidity. However in the past few years it has become clear that we are on the verge of a major public health crisis as bacterial resistance to many of the routine antibiotics is nullifying their effects and benefits. The Director-General of the World Health Organization [1] as well as the Chief Medical Officer of the United Kingdom [2] predicted that the impact of growing resistance will severely impact modern medicine. Our ability to perform routine medical procedures such as joint replacements and cardiac surgery will be curtailed and perhaps most frightening is the emergence of Multi-Drug Resistant (MDR) pathogens which will likely wreak havoc on cancer, transplant and other immunocompromised patients.

In the 75 years since penicillin was discovered, the “golden age” of antibiotic development was in the 1960’s, but in the past decade there have been only two new classes of antibacterial discovered and applied clinically and the number of companies investing in this area is diminishing with only three pharmaceutical firms committed to this problem. Why is that the case?

I suggest the answer is manifold but clearly there are several clear issues; namely lack of clear regulatory guidance for drugs intended to treat Multi-Drug Resistant (MDR) infections, paucity of rapid diagnostics to enable better prescription of antibiotics as well as improved recruitment in trials and finally the economic rationale supporting the exit of firms from the area. Indeed this last reason for the lack of investment in this sector is simple but difficult to address.

There is some encouraging news from both the US Food and Drug Administration (FDA) and European Medicines Authority (EMA). In 2012 the USA the government passed the GAIN Act. This legislation has enabled the FDA to provide channels for companies to apply for Qualified Infectious Disease Product (QIDP) status. This new process enables a fast track review in addition to several post licensing benefits. Further changes to the Federal Register such as the PATH Act are anticipated soon which will enable the agency to provide even clearer clinical trial guidance especially concerning trial size and statistical design [3].

The EMA has for some time been happy to enter into open scientific dialogue with sponsor companies regarding study challenges and designs. Appropriate timely diagnosis of infectious diseases has been fraught with issues for many years. Until the past few years we have employed methods developed a century ago. The advent of nucleic acid amplification tests as well as other highly specific genetically based methods is enabling much more rapid identification of pathogens. These tests are beginning to be approved for broad use but their cost is a major impediment. It is hoped that concurrent research of big

pharmaceutical and the diagnostic companies can accelerate the development and approval pathway.

One of the challenging issues with clinical research in antibiotics has been the number of patients needed to be recruited in order to identify microbiologically documented pathogens in infected subjects. In some infections such as community acquired pneumonia the positive culture rate can be as low as 30%. This leads to increased sample sizes, prolongs enrolments periods and escalates the costs such that many Phase 3 trials can cost over \$80million per study. Thus the use of rapid diagnostic methods will have at least two beneficial outcomes; first clinically, prescribers learn sooner what the causative pathogen is and in some cases what is the resistance pattern thus allowing appropriate therapy from the outset. Secondly, the use of these rapid diagnostics should improve enrolment in clinical trials thus accelerating the process and reducing the costs and timelines. How much impact this will have on the final issue remains to be seen and that is the financial assessment of a new antibiotic.

The economics of pharmaceuticals has been a matter of some contention especially in these times of global recession and frugality. A recent Tufts analysis of drug development suggested that it now costs over \$2 billion to bring a drug to the clinic [4]. It is assumed that certain types of drug are “worth” the prices being charged notably oncologic agents which may cost many thousands of dollars. The recent launch, and approval in the UK of the antiviral as a cure for hepatitis C, sofosbuvir (Solvadi), has caused a storm in the US. The price set for this treatment of HCV ranges from \$84,000 in the USA to £70,000 in UK. However this drug cures HCV, a previously lifelong condition which had many serious sequelae such as liver transplant and many hospitalizations.

It is this life saving ability of antibiotics which has been over-looked, clearly the impact antibiotics have is marked in terms of saving lives or simply getting people back to work sooner. Yet the general perception is that antibiotics are a routine commodity. The pharmaceutical industry evaluates every potential drug in terms of potential earnings over the probable life of the drug, ranging from 10-15 years. The calculation is termed the net present value (NPV) which in almost every case for antibiotics is negative, unlike cardiac or other lifelong drugs. The main driver of this problem is that we have been very successful at reducing the number of daily doses of antibiotics and they are taken over a shorter duration. Thus the pill load is much reduced, making it even harder to recoup invested resources, which with an antibiotic can be over \$800 million over a 5-8 year period.

Combine these economic hurdles with escalating appropriate (but diminishing) use or stewardship of antibiotics and we have a conundrum. Indeed almost any new antibiotic is reserved to a last resort choice in order that “we protect it from resistance development”.

How do we provide the pharmaceutical industry with adequate, long-term incentives to return to this essential therapeutic area? Public

perception of antibiotics is poor partially driven by certain pharmacy chains in the US actually giving away the “top 10 antibiotics” as loss leaders. The purpose of this practice is to entice shoppers to spend in other parts of the pharmacy. Equally in many parts of the developing world antibiotics can be bought over the pharmacy counter or at local markets, often in small doses or courses because that is all the patient can afford. So the big question is how we balance the books to encourage companies like Actavis, The Medicines Company, Merck, Roche or Cubist to invest in this field. Indeed in 2013 Cubist invested over \$400million in antibiotic research and development to continue to find and develop effective and safe new agents to treat the burgeoning incidence of MDR pathogens.

The value of antibiotics which are shown to be effective in treating MDR infections should receive some of the benefits given to orphan drugs and receive tax credits and given patent protection. Moreover they could be priced in a similar bracket to the orphan agents. If we do not recognize this situation and empower the regulators around the

world to give guidance which can establish initial efficacy and then post-approval the safety of the drugs are established. If we do not react soon we may find that we are quickly returning to the 1930’s again. Fortunately there are some academic units still committed to the field but even their interest could wane if the final product is not developed. Pogo said “we have seen the enemy and it is us” [5] he may have been right concerning antibiotics and their future development.

References

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