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Research and Development of Antibiotics: The Next Battleground

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ABSTRACT: Antibiotic research has been hindered by a perfect storm consisting of scientific challenges, regulatory uncertainties, difficult markets, and industrial consolidation. At the same time, antibiotic resistance is making the medical need for a robust antibiotic pipeline ever more urgent. The Food and Drug Administration in the United States, following their European colleagues, has made important progress in correcting its position as part of this perfect storm and in providing less expensive and streamlined pathways for antibiotic development. But the economics of antibiotic development and marketing remains a potential stumbling block to reinvigorating antibiotic research within the pharmaceutical industry. The current situation is reviewed in this viewpoint article.

Research and development of new antibiotics, as a field of endeavor, has endured the perfect storm for the last two decades.[1] The perfect storm is defined by the following trends. (1) The discovery of new, useful molecules has become more and more difficult, partly because the greatest medical need is therapy for Gram-negative infections. The Gram-negative bacilli have a challenging dual-membrane system and an army of efflux pumps against which scientists must do battle. (2) The marketplace for antibiotics is highly saturated and genericized, and achieving adequate reimbursement and therefore return on investment has become ever more challenging. (3) Regulatory bodies, mainly the United States Food and Drug Administration (FDA), went through a prolonged period where the clinical trial requirements for most infectious disease indications were rendered infeasible. (4) The continued megamergers within the pharmaceutical industry coupled with the outright abandonment of antibiotic research for the above reasons have led to a critical diminution of researchers and research in the area. In my view, the growth of antibiotic research in biotech has failed to compensate for this loss.

The 1990s was the genomics era in the pharmaceutical industry and within antibiotic discovery in particular. Bacterial genomes were more cheaply and rapidly sequenced than was the human genome. Most of the large pharmaceutical companies invested in some form of bacterial genomics research in the hopes of identifying new targets for new classes of antibiotics.[2] Alas, these efforts came to naught, and the entire endeavor was abandoned by the end of that decade.

The discovery of new classes of antibiotics remains extremely challenging, and only three have been approved since 1999—linezolid, daptomycin, and most recently avibactam, a novel B-lactamase inhibitor. Although linezolid and daptomycin target Gram-positive pathogens, avibactam, combined with ceftazidime, takes aim at resistant Gram-negative bacilli. All were discovered using traditional methods and not genomics.

The FDA missteps include requiring an increased stringency for the typical types of clinical trials, noninferiority trials, used for the development of antibiotics. This is so because it is not ethical to withhold efficacious therapy from patients; therefore, you cannot treat patients with potentially serious infections with a placebo. Hence, superiority trials have, in general, been impossible to conduct for new antibiotics. But the increased statistical stringency meant that much larger numbers of patients had to be studied to support FDA approval. The increased costs put further pressure on the industry's requirement to show a return on investment. Following the so-called Ketek scandal of 2006,[1] the FDA began issuing clinical trial guidance for antibiotic trials that were simply not possible to implement. Seeing that it would not be possible to develop antibiotics for the U.S. market, companies accelerated their march to the exits.

The two most important events of the last 20 years of antibiotic development were (1) the descent of the FDA into the abyss of infeasible antibiotic trial requirements and (2) its subsequent realization, in 2012, that its policies regarding the development of antibiotics were misguided and were contributing in an important way to the perfect storm.[3] The FDA began a "reboot" process at that time that appears to have been very successful. Although I retain some reservations about several of their trial requirements, overall the FDA has come a very long way, and this has been recognized by the industry. Key changes in the FDA's approach, mostly shared by their European regulatory colleagues, include the following examples. (1) The regulatory authorities have streamlined traditional development pathways, allowing for approvals in two different indications with only two trials. All of these new approaches emphasize the importance of preclinical data including a strong pharmacokinetic and pharmacodynamic basis for the proposed clinical trials. Examples of the new approaches include allowing a single trial in complicated urinary tract infection and one in complicated intraabdominal infection to provide for approval in both indications whereas previously two trials in each were required. This move more than halves the time and expense to obtain these market approvals. Another example would be that one trial in complicated skin and soft structure infection (now called acute bacterial skin and soft tissue infection by the FDA) plus one trial in community-acquired pneumonia are now enough to achieve approval in both indications. Again, two trials in each were required previously. (2) There are now very

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streamlined pathways that allow for the development of antibiotics for unmet needs, i.e., highly resistant infections where treatment choices are limited or nonexistent.[4] The safety database for such a trial could be as small as 300 subjects treated. Just this year, the FDA approved Actavis/AstraZeneca's ceftazidime-avibactam, a novel B-lactam-B-lactamase inhibitor combination, for the treatment of infections where other treatment choices are limited or do not exist mainly on the basis of clinical phase II data. This approval establishes a revolutionary historical precedent in the development of antibiotics and shows that the FDA has become seriously engaged in bringing needed antibiotics to patients and physicians.

With the reboot at the FDA, some in the industry have been putting their toes back in the waters of antibiotic research. Sanofi-Aventis, after having spun out virtually all of their key antibiotic assets and their researchers in 2004, re-established an antibiotic research group around 2009. Roche re-entered antibiotic research within the last 2 years or so. Although these moves have been positive, AstraZeneca recently announced its departure at least from the research end, although they will continue their development of certain products. With their purchase of Cubist, Merck proceeded to close the Cubist research site and fire the Cubist antibiotic researchers there. It is thus clear that the industry has mixed interpretations of the new opportunities in antibiotic research.

What accounts for these disparate views within industry? It is their continued worry about their ability to provide a return on their investment in antibiotic research. Although the management at Sanofi-Aventis and Roche clearly see antibiotic research in an optimiztic light, the CEO of AstraZeneca has the opposite view.

Our next great challenge is to provide mechanisms such that he and all captains of industry see that antibiotic research is a promising way to provide needed medicines for patients and their physicians while boosting the corporate bottom line. How can we make sure that investments in antibiotic research are rewarded? A number of approaches have been suggested recently.[5,6] First, the provision of nondilutive funding for research and development including, and perhaps especially, for the expensive pivotal clinical trials required for registration and marketing. Until now, the Biomedical Advanced Research and Development Authority in the U.S. and the Innovate Medicines Initiative in Europe have provided these funds. The National Institutes of Health in the U.S., the British Research Council in the U.K., and the European Commission in Europe have all provided funding in the form of smaller grants for antibiotic research, usually at preclinical stages.

Second, pull incentives that would begin at the time of market entry could be an important way forward. Possible approaches to this have been discussed. (1) Guaranteed purchase for the first several years after market entry is probably the most likely pull incentive to receive government support. (2) Prizes have been mentioned. (3) Patent vouchers or the so-called wild card patent exclusivity extension have been proposed for a number of years. In this case, a company, say Pfizer, could, upon approval of a needed new antibiotic, request and receive an additional 6 months to 2 years of sales exclusivity—protection from generic intrusion—for a product of their choice. This could have been, for example, Lipitor that sold for $15 billion annually at its peak. (4) Simply charging and being reimbursed at high prices, similar to what Gilead just accomplished for their Hepatitis C inhibitor, Sovaldi is the most likely American solution. (5) A mixture of the above could be fashioned depending on the individual needs of any particular market.

Some have termed the postapproval pull incentives "de-linking" mechanisms, suggesting that they would provide a way for companies to reduce marketing expense.[6] In this way, some believe, there would be less inappropriate use of antibiotics and therefore less selective pressure leading to more resistance. But I think this view is misguided. Even appropriate antibiotic use—and the vast majority of use in hospitals is appropriate—will continue to select for resistance.

I think these mechanisms simply provide a way for the industry to gain its required return on investment through the recognition of the value of the drugs they are bringing to market. We as a society must more appropriately value antibiotics as the life-saving drugs that they are. What other types of drugs actually cure disease? Not many, I would say. Most drugs for cancer prolong life for how long? Three months? Six months? Data indicates that very high prices for drugs active against resistant strains can be justified based on years of quality life gained via their potential to save productive lives, to lower the morbidity of serious infection, and to get patients home from the hospital earlier than would otherwise be the case.[7]

In conclusion, I would say that the economic gauntlet has now been thrown. We must find a way to appropriately value antibiotics, and we must do so now.

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Notes

The authors declare no competing financial interest.

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