Public comment by John H. Rex, MD
Plazomicin Sulfate Injection
2 May 2018 Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC)

Introduction: I would like to thank the Agency and the Committee for allowing an opportunity for public commentary during this meeting of the AMDAC. I can't attend in person, hence this written comment.

As background, I am an internist with 30 years of development and policy experience focused on antimicrobial agents. A summary of my background is found in the section below entitled *About the Author*.

For avoidance of doubt, my conflicts of interest relative to today's discussion are summarized here. I moved from academia to industry in 2003 with the specific intention of working to ensure that modern medicine had a robust, diverse, and developable pipeline of useful new antibiotics addressing the rising tide of antimicrobial resistance. Because of that decision, I now do own stocks and have investments in companies that are developing a range of antibacterial and antifungal products. As one example of this, I am the Chief Medical Officer of a company focused on developing a novel mechanism antifungal agent.

Pertinent to today however, I have no affiliation with the sponsor of plazomicin and I am not being reimbursed for my comments. While preparing my comments, the sponsor shared both a copy of the sponsor's briefing book and the draft version of FDA's briefing document received by the sponsor on 10 Apr 2018.

Comments: I will focus my comments on the sponsor's efforts to develop comparative data on plazomicin vs. colistin-based therapy for CRE bloodstream infection. I would like to make these points:

1) The data on plazomicin have flaws.
2) Use of a 28-day mortality outcome addresses many of these flaws.
3) It is not possible to develop more or better data.
4) It is bad for public health if it is possible to develop more or better data.
5) As a community, we must work with this paradox rather than struggle in vain against it.

1) **The data on plazomicin have flaws.** These are doubtless obvious by now. Yes, the sample size is small. Yes, the blood culture at the time of enrollment was not always positive. Yes, there were adjunct therapies.

2) **Use of a 28-day mortality outcome addresses many of these flaws.** Consider carefully the impact of the use of 28-day mortality as the endpoint. This is as strong a measure as exists: It is unambiguous, it does not require adjudication, and it has clear relevance to the patient.

3) **It is not possible to develop more or better data.** A larger sample size might also have helped address those flaws. But, Achaogen noted in a recent presentation that (a) 2,109 subjects were screened to enroll these 69 and (b) the study cost approximately $1m/enrolled patient. Why was this so hard? Why was Achaogen unable to meet its initial goal of enrolling several hundred subjects? Well, for this we must turn to the next point…

4) **It is bad for public health if it is possible to develop more or better data.** The low enrollment in the bloodstream study was not due to lack of effort or failure to go to sites that had seen cases of CRE. As has been the case for similar efforts (e.g., a study of a new beta-lactam–beta-lactamase inhibitor that enrolled 77 subjects during a 3-year study of CRE infections, https://clinicaltrials.gov/ct2/show/NCT02168946), Achaogen ran into the Multi-Drug-Resistant Bacteria Center of Excellence problem. Health care facilities are not happy if the billboard in front declares "We have high rates of infection due to MDR pathogens … but come on in as we have clinical trials for this!" Rather, intensive efforts go into Infection Prevention such that sites that once had a high rate now have a much lower rate.

   This is a good for everyone: if it is easy to enroll a trial of this type, something has gone terribly wrong. Further, keep in mind what happens as a few new drugs are registered. The bar for the next drug goes up –

and this is again a good thing. But, it also means that future drugs will not be able to develop data even this strong. And, the likelihood that this sponsor can generate more data is equally low.

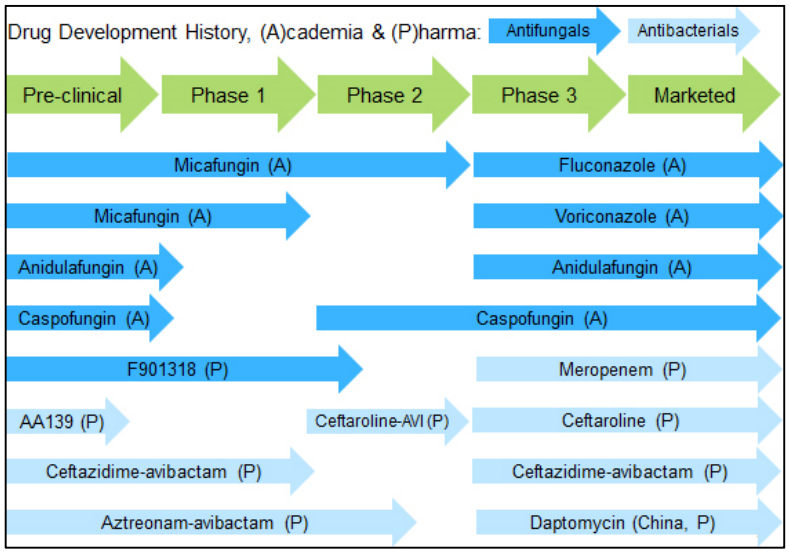
In short, we as a community want it to be nearly impossible to generate data of this type. CDC is going to continue to reduce rates of CRE. Infection Prevention practices will continue to improve.

5) **As a community, we must work with this paradox rather than struggle in vain against it.** We desperately need a robust pipeline of new drugs for bad bugs. And while we'd like to always have clean and easily interpreted data on new agents in the setting of MDR/XDR pathogens, it is important to balance this vs. the art of the possible. What's been done here is one example of that balance. Key lessons are (a) large data sets should be uncommon, (b) the data that can be generated have both human and financial costs, and (c) every scrap of data from trials like this needs to be made available to prescribers.

In summary, Achaogen's efforts to generate data on their product both in the setting of Usual Drug Resistance (UDR, the cUTI trial) and in Multi-Drug Resistance (MDR, the bloodstream infection trial) have been appropriate and diligent. Their limited ability to enroll the bloodstream trial is good for the community and you should (hopefully!) expect future drugs to have even more difficulty with showing outcomes in the MDR/XDR setting. As a community, we need to find a path to labeling that reflects these tensions.

About the Author: John H. Rex, MD, is a physician and drug developer with ~30 years of development and policy experience focused on antimicrobial agents. He is currently CMO for F2G, Ltd. (an antifungal biotech), is on two biotech boards (F2G Ltd, Adenium Biotech ApS), supports a charitable foundation (Wellcome Trust), is an operating partner with a venture capital group (Advent Life Sciences), and is a voting member on the Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB). He also blogs regularly at http://amr.solutions/blog.html.

His experience (figure) includes moving compounds from early preclinical development through all development phases via academic positions (NIH, Bethesda, MD; Univ. of Texas Medical School-Houston) and VP-level roles at a multinational pharmaceutical firm (AstraZeneca). Other past activities include advancing novel regulatory paradigms for antibacterial agents,[1,2] publications on novel reimbursement models for antibiotics,[3] support of a public-private partnership (CARB-X), founding of the New Drugs for Bad Bugs (ND4BB) program of Europe's Innovative Medicines Initiative (IMI), and a 4-year term as Industry Representative on the FDA Anti-Infective Drugs Advisory Committee (AIDAC, 2007–11).



1) Rex JH et al. Proposal for a comprehensive regulatory framework to address the unmet need for new antibacterial therapies. Lancet ID 13:269-275, 2013.
2) Rex, JH et al. Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. Clinical Infectious Diseases 65:141-146, 2017.
3) Rex, J. H. and K. Outterson Antibiotic Reimbursement in a Sales-Delinked Model: Context and a Benchmark-Based Global Approach. Lancet ID 16:500-5, 2016.