

**October 30, 2014**

**Achaogen's Responses to Followup Questions on Dr. Kenneth Hillan's Testimony to the House Energy and Commerce Committee Subcommittee on Health on "21st Century Cures: Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development"**

**The Honorable Joseph R. Pitts**

- 1. What are other countries or the European Union doing to help spur research and development for anti-infectives? Which initiatives are working well and which will likely have the most significant impact to draw more companies to anti-infective product development moving forward?*

On the regulatory front, the EMA, similar to the FDA, has issued new guidance documents related to antibacterial drug development which describe streamlined pathogen-focused development pathways based on smaller clinical datasets. The feasibility of these approaches remains to be tested. The EMA is also piloting an adaptive licensing program (not specific to antibiotics) that will allow for early approval of drugs intended to treat conditions for which there is a high unmet medical need. Using existing EU regulatory mechanisms, an Initial approval would be granted for a limited patient population followed by subsequent approval(s) for a broader population based on postmarket trials and real-world data. We believe that an adaptive approval approach could have a positive impact on anti-infective product development. The passage of the ADAPT Act allowing a limited population approval would be an important step forward in facilitating this type of approach in the US.

On the research and development front, the EU and US independently have created excellent public-private partnerships that support antibacterial R&D, however the access to European R&D funding is restricted. The Innovative Medicines Initiative (IMI) funds antibacterial R&D and coordinates in-kind support from European pharmaceutical companies, but this funding may only be spent in EU member and designated associate countries. American researchers are not eligible for IMI funding. Conversely, in the US, the Biomedical Advanced Research and Development Authority (BARDA) generally has no such geographic restrictions. We support funding antibacterial R&D based on merit, regardless of where it is being performed.

Regardless of geographic location, any incentives that increase revenue potential, reduce product development costs, or ease regulatory requirements will stimulate R&D. We believe that the most effective incentives will be those which help manufacturers achieve sustainable commercial returns on new antibiotics. Examples of such incentives are noted in our answer to Ms. Blackburn's question below. Given the long development timelines for antibiotics, companies must know that these incentives are stable and not subject to decreases in funding. These incentives must have clearly defined budgets and protections to assure companies that they will be available tomorrow if companies choose to invest in antibiotic R&D today.

**The Honorable Marsha Blackburn**

1. *Our committee has enacted important reforms like the GAIN Act to stimulate development of new antibiotics, but realize more work needs to be done. It is my hope that as part of the 21<sup>st</sup> Century Cures effort we will put additional incentives in place for antibiotics that are designated as Qualified Infectious Disease Products (QIDPs). What other specific incentives do you recommend Congress consider for FDA designated QIDPs?*

We recommend that the Committee consider the following specific incentives for QIDPs:

1. Reimbursement reform to allow antibiotics to be priced at a level commensurate with their value to patients. The DISARM Act would reform reimbursement of qualifying antimicrobial products in the hospital setting for Medicare/Medicaid patients. We encourage the committee to also address reimbursement for patients covered by private insurance by authorizing a supplemental government payment to the hospital for certain QIDPs on top of the reimbursement payment made by the private insurer.
2. Transferrable market exclusivity vouchers. Companies that develop new antibiotics should be awarded a transferrable voucher for several years of market exclusivity. The antibiotic developer could either apply the voucher to one of its other products in a more commercially attractive therapeutic area such as diabetes, cardiology, or oncology, or in the case of a company like Achaogen whose sole focus is on antibiotics, could sell the voucher to another company that is interested in applying the voucher to another product.
3. New FDA approval pathways that allow for faster approval based on limited clinical data sets (e.g., the ADAPT Act).
4. Increased federal R&D funding, e.g. through BARDA and NIH, beginning with early research efforts to discover new antibiotics and continuing through late-stage clinical trials and FDA approval. The funding must be sustained throughout the entire development timeline for each new antibiotic.
5. Incentive payments (e.g., prizes and advance market commitments) that would be made as the QIDP meets certain development milestones. For example, payments of increasing dollar amounts would be awarded upon IND filing, completion of phase 1 clinical trials, evidence of efficacy clinical trials, FDA approval, etc.
6. Increased FDA flexibility and reimbursement reform for diagnostics intended for the safe and effective use of antibiotics. As technology evolves very rapidly, the FDA must take a nimble approach to approve new assays and instrumentation in a way that does not hold up the approval and use of new antibiotics. Diagnostics intended to be used in this manner should be approvable based on a dataset similar to that currently required for the existing 510(k) clearance pathway. Such diagnostics should also be considered in DISARM and other reimbursement reform measures.

We recognize that Congress faces pressure to limit the budget impact of new legislation, and that extending these incentive to all QIDPs may increase expenditures to a level that may reduce the

likelihood of passage. To control costs, QIDPs should be sub-categorized, with the highest incentives given to those that address the most serious unmet medical needs.

- 2. Congress via the GAIN Act gave FDA a very important tool to designate certain anti-infectives as QIDPs; and the agency has made good progress on QIDP guidance, as well as designating over 30 developmental antibiotics as QIDPs. If we create other incentives as we should-- -real incentives are needed --we must avoid a situation where there is confusion and differences over what qualifies for which type of incentive across different agencies of HHS. Will you respond to this statement?*

We agree that we must avoid confusion about which products qualify for various designations (e.g., QIDP, Fast-Track) and which incentives are associated with each designation. While it would be easiest if there were a single designation associated with all incentives, we believe that *further sub-categorization* may actually be necessary to ensure that the greatest incentives go towards antibiotics that address the most serious unmet medical needs. The specific incentives associated with each designation must be communicated very clearly to all stakeholders, including manufacturers, physicians, and pharmacy directors, so that we can understand and track the incentives.

### **The Honorable Michael C. Burgess**

- 1. When a small company considers early-clinical stage products, when does that company begin to weigh the cost of development, potential market size, and price point it would be able to achieve? I am presuming that many antibiotic products are left in the labs because there is limited ability to ever make the products profitable. How critical is product valuation to your investors?*

As small companies are for-profit entities whose operating capital ultimately depends on the proceeds from sales of products, the potential profit that a new antibiotic product could generate is critically important to company management and investors, and is considered at several stages of a company's life cycle. First, entrepreneurs seeking to form companies to address antibiotic resistance face a difficult challenge in raising funding from venture capitalists. According to a 2014 report "Trends in Healthcare Investments and Exits" from Silicon Valley Bank, from 2012-2013 at least 9 therapeutic areas attracted more new investment money from the 15 most active biopharmaceutical venture capital investors than anti-infectives. The therapeutic areas in which venture capitalists are investing, including oncology, cardiovascular diseases, and metabolism, all present greater potential return on investment than antibiotics, largely due to products in those therapeutic areas having greater commercial potential. Second, at the early research phase, small companies must devote their limited research dollars and human resources to the discovery programs most likely to generate product candidates that will provide a return on investment. This leads to management prioritizing research programs in other therapeutic areas over antibiotics, and in antibiotics that offer the best potential commercial returns over antibiotics where there may be an unmet medical need but no potential future profit. NIH budget constraints have led to a dearth in government funding for early stage antibiotic discovery research, leaving a critical funding gap for such early-stage discovery research. Finally, the cost of conducting clinical trials – particularly Phase 2 and 3 trials – is substantial, and products selected for clinical development must

generate a return on the upfront investment that companies must make to conduct clinical trials. Thus, profit potential is critical at every stage in the development of new antibiotics.

### **The Honorable Gene Green**

- 1. You mentioned in your testimony the importance of the innovative trial design for your CRE drug that was agreed upon with the FDA. How important is it for developers in your space to secure assurance from the FDA on trial design as early in the process as possible?*

FDA guidance relating to the development of new antibiotics has changed repeatedly over the past several years, and manufacturers have become concerned that their planned clinical trials will not meet the FDA's requirements for approval. A high-profile example where this has happened is that of the new antibiotic telavancin. Theravance was conducting Phase 3 clinical trials of telavancin in hospital acquired pneumonia (HAP) when FDA changed their guidance to require different endpoints than what were required when the clinical trials began, and FDA initially denied approval of telavancin for HAP on the basis that the trials did not meet the endpoints required under the new guidance. While we applaud the FDA for recognizing the need to assure developers that their clinical trial designs will eventually support regulatory approval, we believe that it is inefficient for the FDA to provide definitive assurance on a case-by-case basis. A better process would be for FDA to provide general guidance for developing new antibiotics that is unchanging, but that allows flexibility in application. Companies should be comfortable that clinical study designs that demonstrate the safety and effectiveness of new antibiotics will be accepted by the FDA without having to secure direct FDA assurance on the acceptability of the trial designs. Under this model, it would still be critical for FDA to be open and accessible to providing consultation to developers on areas where there may be flexibility within the guidance, especially in cases where the antibiotic is intended to fulfill a high unmet medical need.

- 2. Is that an incentive that you believe would help support greater development in the antibiotic space? Why or why not?*

We believe that the lack of commercial viability for new antibiotics relative to other therapeutic areas such as oncology or endocrine diseases is currently the greatest barrier to the development of new antibiotics. As discussed in our responses herein, government incentives that increase revenue potential (DISARM Act, market exclusivity vouchers), reduce development costs (increased R&D funding, milestone-based "prizes"), or reduce regulatory requirements (ADAPT Act, greater FDA flexibility) will offer the greatest incentive for new antibiotic development.