Written Testimony of
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Subcommittee on Health
Committee on Energy and Commerce

United States House of Representatives
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Examining Ways to Combat Antibiotic Resistance and Foster New Drug Development

Introduction

Thank you, Chairman Pitts, Ranking Member Pallone and members of this important Committee for this opportunity to come before you today to discuss the current antibiotics crisis and strategies for reversing its course. I am Dr. Adrian Thomas, vice president of Global Market Access and head of Global Public Health at Janssen, the pharmaceutical companies of Johnson & Johnson.

On behalf of the Johnson & Johnson Family of Companies, I applaud you for organizing this hearing, and commend all those leaders in this room and well beyond it who have given voice to the growing threat of antibiotic resistance.

It is my privilege to be able to view the issues at hand from the standpoint of more than 30 years of experience in public health—from my early career in Australia's Flying Doctor Service, providing emergency care to the rural poor, to my current role overseeing Janssen's global portfolio of products and services for diseases of high public health impact, including HIV, tuberculosis, and Ebola. I am a clinical pharmacologist and vascular physician by training, with additional expertise in pharmaceutical safety surveillance, epidemiology, clinical trial design and methodology. The majority of my 17 years in the innovator pharmaceutical industry has been spent at Johnson & Johnson.

Headquartered in New Brunswick, New Jersey, Johnson & Johnson is the world's largest and most broadly based healthcare company. Our company was founded more than 125 years ago

with the initial aim of creating clean and safe conditions for patients undergoing surgery. Those early innovations in antiseptic surgery represented a major leap forward in healthcare. Today, our Company's quest for similarly transformative advances in healthcare remains vibrant, spanning many categories of products and services relevant to the topics of today, among them medical device and diagnostic technologies, consumer healthcare products, and pharmaceuticals.

Fundamental to our strategy is participation in and investments across the healthcare innovation ecosystem. We seek out the best science wherever it may be, accelerating cutting-edge projects at universities, academic institutes, and small start-up companies around the world. Our place and perch in this ecosystem lends us important insights into the number and status of projects in areas of unmet medical need—including antibiotics. Our in-house capabilities in the research and development (R&D) of new products, such as at Janssen, the pharmaceutical companies of Johnson & Johnson, lends us a deep understanding of the costs and risks associated with biomedical innovation.

Janssen Global Public Health, lessons from the SIRTURO™ experience

One of the groups at Janssen that I oversee, Janssen Global Public Health, is responsible for a particular medicine, known by its trade name as SIRTURO™, worth highlighting here. SIRTURO™ is a new antimycobacterial drug indicated as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis, or MDR-TB. It is the first new medicine for TB with a new mechanism of action to be developed in more than 40 years, and is the first new drug specifically indicated to treat a drug-resistant form of tuberculosis. We commend the U.S. Food & Drug Administration (FDA) for the great care it took, and continues to take, in providing guidance throughout the product's development process.

In keeping with the special requirements FDA and other regulatory agencies have set for SIRTURO™, our company's post-marketing commitments are substantial. They include a lengthy Phase 3 research program; a pediatric formulation and first-ever randomized, open label, controlled clinical study in a pediatric MDR-TB population; and a 5-year prospective study to characterize the acquisition of resistance to this new drug. Our experience with SIRTURO™ highlights the breadth of post-approval responsibilities and the magnitude of sustained investments required to ensure appropriately its safe and effective use worldwide. We estimate that approximately half of all investments necessary to develop and support SIRTURO™, amounting to several hundreds of millions of dollars, will be required *after* the point of U.S. regulatory approval in December 2012.

These are investments for which we expect no "return" as the term is traditionally defined. Normal cost recovery and profit-deriving sources for the pharmaceutical industry are well characterized and continue to rely on advanced-economy markets with more equitable and advanced healthcare systems. However, MDR-TB case numbers in the U.S. and EU amount to fewer than 2,000 patients per year. In the United States, fewer than 150 cases are reported annually. As is the case with most therapies developed for neglected diseases, cost recovery and profits associated with eventual sales of SIRTURO™ will prove to be relatively small, elusive, and insufficient to cover the costs accompanying the drug's introduction.[1]

Our experiences with SIRTURO™—today and since its discovery in our labs more than a decade ago—illustrate just some of the challenges associated with the development and introduction of new antibiotics, particularly those addressing an area of great need: namely, drug-resistant infections which, even if not yet commonplace, represent a significant health threat.

These challenges help to explain why the overall state of antibiotics R&D is deficient relative to the need. They also point us to potential policy options for overcoming and counterbalancing current risks specific to antibiotics development. Today, the innovation climate for antibiotics and other antimicrobial R&D remains suboptimal, even despite laudable recent efforts to improve it. The basic science associated with this field continues to prove exceedingly difficult, with high rates of failure.

The dangers in view

Failure, it seems, is no longer an option in the wake of the critical and growing public health threat that antibiotic resistance poses. The emergence of so-called Superbugs, or drug-resistant bacteria, forces our attention to the inadequacy of our therapeutic arsenals. Management of hospital and healthcare-acquired infections costs the U.S. health system an estimated $10MM USD per year.[2] Drug-resistant healthcare-acquired infections (HAIs) are on the rise, imposing further costs in dollars spent and lives lost. Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major public health threat globally, even as notifications of other multidrug-resistant

[1] Our company received a Priority Review Voucher with the accelerated approval of SIRTURO™. The voucher program marked an important step forward in the design and implementation of new incentives to spur R&D in areas of high unmet medical need. At the same time, the program provides limited incentive to invest in high-risk early research into innovative therapies because, in considering such investments, the voucher value is discounted both by the high risk of program failure and the substantial delay (typically over a decade) before the voucher would be received. We believe the Priority Review Voucher would be most effective as an incentive for innovator firms if it were part of a more complete, diverse and integrated set of incentives that Congress can help to make available.

[2] Goodman, Brenda. "Hospital-Acquired Infections Cost $10 Billion a Year: Study." *US News*. U.S.News & World Report, 03 Sept. 2013. Web. 16 Sept. 2014.

Gram-negative organisms continue to increase (e.g., Acinetobacter baumannii, Klebsiella pneumonia, Enterobacter aerogenes).[3]

Absent new treatments or vaccines, we stand all but defenseless against these dangers.

Numerous programs have been put into place to help keep drug-resistant bacteria at bay. We commend the U.S. Centers for Disease Control and Prevention (CDC) for its leadership in this regard. Johnson & Johnson is proud to work with CDC and other partners in the implementation of such programs to reduce HAIs in the U.S. and abroad.[4]

While strategies for preventing the spread of drug-resistant bacteria in healthcare settings—and for better management of and stewardship over antibiotics on the market—are vital in the fight against resistance, *we believe that current conditions demand an even greater focus on stimulating R&D on new antibiotics and adjacent technologies (e.g., diagnostics)*. Creating a special framework for innovation in antibiotics R&D, sufficient to attract the world's best and brightest to this great challenge, must be a major point of focus as we examine solutions to the current crisis.

Lessons and warnings from the Ebola crisis

This morning's hearing is timely as tragedy unfolds in West Africa with the Ebola outbreak that has infected and killed more people than all previous Ebola outbreaks combined.[5] Though Ebola is treated with antivirals, not antibiotics, this outbreak presents important lessons that merit our attention.

The presence of the Ebola virus in West Africa is not new, but years of neglect and a variety of armed conflicts have dramatically weakened the infrastructures, including health systems, in impacted countries. Considering the topic of this discussion today, it is useful to consider the importance of multi-pronged strategies to combat and prevent the spread of drug-resistant bacteria, especially where fragile health systems are concerned. Such multi-pronged strategies should include, for example, attention to both antibiotic innovation and stewardship.

Also relevant to today's topic are the biosecurity concerns that Ebola brings into view. While it is generally believed that the Ebola virus is limited to human transition through contact with the

[3] Pollack, Andrew. "A Rising Hospital Threat." *The New York Times*. The New York Times, 26 Feb. 2010. Web. 16 Sept. 2014.

[4] Johnson & Johnson is currently working with Advanced Sterilization Products to pioneer the reduction of pathogens from health care settings with GLOSAIR™ area disinfection products.

[5] Cook, Nicolas, and Tiaji Salaam-Blyther. *Ebola: 2014 Outbreak in West Africa*. Rep. no. 7-5700. Washington DC: Congressional Research Service, 2014. Web. 16 Sept. 2014.

blood, secretions, organs, or other bodily fluids of already infected patients, the epidemiological data clearly demonstrate that Ebola can cross borders as easily as any traveler unwittingly incubating the disease. Our world's advanced transportation systems facilitate the exchange of sickness as well as that of people and goods. Viewed in this context, the Ebola outbreak is clearly a national security issue for many countries.[6]

At present, there are no drugs proven to prevent or treat infection with the Ebola virus, despite its documented emergence nearly forty years ago in 1976.[7] Health experts can control it under favorable infrastructure conditions, but those are sorely lacking in the developing nations where the virus's spread has reached crisis proportions. On an emergency basis, several experimental therapies have been used that show significant promise. The absence of ready, proven therapeutic and other tools to fight this virus leaves the world at large at a loss.

At Johnson & Johnson, we have added our own resources and commitment to this critical endeavor. With the support of funding partners such as the National Institutes of Health (NIH), we are fast-tracking the development of a potential new combination vaccine to help protect people against the Ebola virus.

Our determination notwithstanding, the hurdles to our success are considerable. Beyond the extremely challenging science involved in development, inadequate market- and policy-derived incentives for investments of this type and scale compound the difficulties in play.

Similar difficulties plague the antibiotics space.

Reshaping the incentives paradigm for antibiotics R&D through policy

The development process for any innovative therapy is recognized for its cost, risk, complexity and lengthy duration. Importantly, innovators must absorb the economic impacts of failures in the R&D process, sometimes amounting to hundreds of millions of dollars or more. Less than one in every 10 drug candidates entering Phase I clinical trials ever makes it to market.[8] Extensive and expensive clinical testing is necessary and, for those drugs that do succeed to the point of market approval, post-market research requirements can be extensive and costly.

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[6] *Ibid*., page 3.

[7] *Ibid*., summary page.

[8] Herper, Matthew. "The Truly Staggering Cost of Inventing New Drugs." *Forbes*. Forbes Magazine, 2 Oct. 2012. Web. 16 Sept. 2014.

The distinctiveness of pharmaceutical R&D for drug-resistant infectious disease places new points of strain on this already challenging innovation model. The development shift forced by drug resistance demands a targeted approach that is very different from approaches employed for broad-spectrum antibiotics in the past. Failure risks and rates are higher than average.

For these reasons and more, the current incentive structure for antibiotics is simply too ill-fitting and anemic to stimulate the level of new antibiotic R&D investments so critically needed to strike back at drug-resistant infections.

Changes in public policy toward the creation of a new incentives framework specific to antibiotics R&D can help to offset these challenges. As it has done for other areas and industries, the U.S. can lead the world in creating the enabling conditions for progress toward new antibiotics, and in so doing can affirm its role as the world's preeminent driver of biomedical innovation. In recent years, the U.S. has already made important strides toward this end.

The GAIN Act: An important first step

This Committee, Congress, and the president have all recognized the importance of infusing new incentives into the development of needed antibiotic therapies, evidenced by the "Generating Antibiotic Incentives Now," or "GAIN" Act, signed into law in 2012 as part of the *Food and Drug Administration Safety and Innovation Act*. The GAIN Act adjusted the existing incentive structure for manufacturers by extending the term of market exclusivity for an additional five years on new antibacterial or antifungal drugs for use by humans intended to treat serious or life-threatening infections, when designated under the law as "qualified infectious disease products." Today, some companies have been able to take advantage of the new investment incentives provided by the extended market exclusivity period, and have advanced some potentially promising new options through the earlier stages of the drug approval process.[9]

In this way and others, GAIN was an important first step toward a more comprehensive restructuring of the incentive model for antibiotic R&D.

Appropriately, this Congress has carried the baton forward with a variety of new legislative proposals aimed at combating antibiotic resistance. Bills introduced in recent months include the ADAPT Act, DISARM Act, and STAAR. It is our hope that this Committee and the Congress will give serious consideration to each of these proposals. Beyond these proposals, we believe

[9] PEW Charitable Trusts. "GAIN: How a New Law Is Stimulating the Development of Antibiotics." *pewtrusts.org*. PEW Charitable Trusts, 7 Nov. 2013. Web. 16 Sept. 2014.

there remains a need for Congress to put forward a bolder and more comprehensive set of "push and pull" incentive options specific to antibiotics.

Toward a broader, bolder "basket" of incentive options

For drug-resistant diseases especially, the need for more R&D across the board remains stark. To address this need, we must explore an array of options for stimulating antibiotic drug development, and the development of adjacent technologies such as companion diagnostics. In short, *we must create a broad set of highly attractive incentives to engage many biomedical innovator companies, large and small, in this work.*

Policies should take into consideration a holistic view of the costs and risks required to develop, introduce, and support these products worldwide, and how those costs and risks shift between different actors in the innovation ecosystem at different stages along the pathway, from discovery to development to delivery.

There are many different types of incentive proposals and complementing programs already available for policymakers' consideration. Many worthy options remain in concept form only, yet to be implemented or tested. Until such testing occurs and programs are assessed and refined, the key questions of *what will work?* and *how, when and where will it work best?* will be impossible to answer. Thus, a multidimensional or "package" approach to incentives and programs—allowing innovator firms of all forms to access an assortment of incentives—offers the greatest potential to address various issues facing different organizations and programs at different stages of development.

Such an approach could allow for efficient testing and refining of incentive models; indeed, finding what "works" within an acceptable period of time will almost certainly require testing several options simultaneously.

It is individual innovator companies that are best positioned to assess the likely success of different incentive programs ahead of implementation. Innovators of different sizes and character will almost certainly have varying perspectives on what constitutes an attractive and workable incentive or combination of incentives with regard to various challenges and needed efforts in the area of antibiotic development. Similarly, different types of diseases related to drug-resistant bacteria—each with its own set of risks, markets and cost profiles—will require different incentives as well. Hence, again, the importance of providing a comprehensive package that includes a wide variety of incentive options. It is critical that incentives be designed with an emphasis on pragmatism and with a sense of urgency.

One incentive option meriting focused consideration at the policy level:
Transferable Market Exclusivity

As our company has undertaken its own in-depth analysis of different incentive proposals for antibiotics R&D, it is apparent that many existing proposals offer only marginal valuations ($50-100MM USD) relative to overall R&D costs. Such programs will likely not spur the extent of new innovation required. By contrast, our analysis suggests one potential model as an especially strong option for reinvigorating antibiotics R&D across the spectrum of innovators: namely, Transferable Market Exclusivity (TME).

Transferable Market Exclusivity is a policy incentive that was first proposed in 2003 by Duke University professor and researcher, Henry Grabowski. TME is a pull-based incentive that affords companies a defined period of market exclusivity that can be applied to any compound, thus facilitating R&D spending on a different "socially desirable but unprofitable medicine"[10]

Studies of the Orphan Drug Act have demonstrated that the single most valuable aspect of the act was guaranteed market exclusivity.[11] In the decade before 1982, FDA approved 10 treatments for orphan diseases, but since 1983 more than 400 products designated as indicated for orphan diseases have been approved.[12] In the past decade, such drugs accounted for 11% of new drug approvals and 24% of biologic drugs. Pediatric exclusivity as implemented under the *Best Pharmaceuticals for Children Act* has similarly proven the value of time-limited exclusivity provisions. Because the opportunity for commercial return on any new antibiotic product itself is so sharply limited,[13] and because the spectrum of innovators required for antibiotics R&D today is so diverse, it is the transferable nature of the market exclusivity period made possible under TME – from one innovator to another, one product to another – that gives this model its unique strength as an innovation driver.

In addition to providing a meaningful incentive to innovators, TME decouples the investment toward development of an antibiotic from the market success of the antibiotic. This decoupling can help to mitigate any tensions between investment recovery and antibiotic stewardship post-market.

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[10] Grabowski, Henry. "Increasing R&D Incentives for Neglected Diseases: Lessons from the Orphan Drug Act." *International Public Goods and Transfer of Technology under a Globalized Intellectual Property Regime*. New York: Cambridge UP, 2005. 457-80. Print.

[11] Peabody JW, Ruby A, Cannon P; The economics of orphan drug policy in the US. Can the legislation be improved? *Pharmacoeconomics*, 1995 Nov; 8(5): 374-84.

[12] "Developing Products for Rare Diseases & Conditions." *FDA.gov*. The Federal Food and Drug Administration, 30 July 2014. Web. 16 Sept. 2014.

[13] For example, by the time of end of market exclusivity, resistance may well have developed, impairing medical and commercial value and thus limiting the value of extended exclusivity of the antibiotic.

We believe that TME can be structured in policy to maximize its public health advantages and to minimize downside risks, including risks to generic manufacturers. So-called "guardrails" could be incorporated into a TME model to ensure, for example, that a TME period or voucher cannot be applied to on-market pharmaceutical products for which fewer than four years of patent life remain.

Facilitating More "Shots on Goal"

Ultimately, we support the inclusion of TME in a larger package of policy incentives for antibiotic R&D because of its clear potential to appeal to a broad swath of innovators and to move them to action. In the design of policies to meet this need of growing magnitude, focus must be fixed on the end goal, namely: more therapeutic and preventive options for patients, sooner. To achieve this, we must foster more "shots on goal," galvanizing and mobilizing the larger innovator community to apply its time, talents and resources to the challenge of antibiotic resistance.

Thank you, Chairman Pitts, Ranking Member Pallone, and members of this Subcommittee, for your leadership on these important issues and your focus on innovation through the 21st Century Cures initiative. I look forward to answering any questions you may have.

Appendix A

Ranking Incentive Models to Drive Innovation and Investment toward New Antibiotics and Adjacent Technologies: Our "Top Three" Recommendations Based on Internal Analysis.

1. Transferable Market Exclusivity
2. Public-sector underwriting of both early- and late-stage development
3. Prize models

Combinations of these and other incentives would help to enlarge the pool of innovators participating in antibiotics R&D.

Less effective incentive models, per our internal assessments: Reimbursement adjustments; tax credits.

Appendix B

The Johnson & Johnson Family of Companies recognizes and applauds the many Members of Congress who have and are leading efforts at the policy level to counter the growing threat of antibiotic resistance.

H.R.4187 - DISARM Act of 2014

Rep. Roskam, Peter J. [R-IL-6]	(Introduced 03/11/2014)
Rep. Davis, Danny K. [D-IL-7]*	03/11/2014
Rep. Bucshon, Larry [R-IN-8]	03/27/2014
Rep. Sanchez, Linda T. [D-CA-38]	03/27/2014
Rep. Jenkins, Lynn [R-KS-2]	03/27/2014
Rep. Gingrey, Phil [R-GA-11]	04/07/2014
Rep. Ellmers, Renee L. [R-NC-2]	05/19/2014
Rep. Gerlach, Jim [R-PA-6]	05/21/2014
Rep. Meehan, Patrick [R-PA-7]	05/29/2014
Rep. Green, Gene [D-TX-29]	05/29/2014
Rep. Buchanan, Vern [R-FL-16]	05/30/2014
Rep. Nunes, Devin [R-CA-22]	05/30/2014
Rep. Larson, John B. [D-CT-1]	06/09/2014
Rep. Pascrell, Bill, Jr. [D-NJ-9]	06/17/2014
Rep. Brady, Robert A. [D-PA-1]	06/17/2014
Rep. Sires, Albio [D-NJ-8]	06/18/2014
Rep. Payne, Donald M., Jr. [D-NJ-10]	06/25/2014
Rep. Lujan, Ben Ray [D-NM-3]	07/29/2014

ADAPT Act

H.R.3742 - Antibiotic Development to Advance Patient Treatment Act of 2013

Rep. Gingrey, Phil [R-GA-11]	(Introduced 12/12/2013)
Rep. Green, Gene [D-TX-29]*	12/12/2013
Rep. Shimkus, John [R-IL-15]*	12/12/2013
Rep. Eshoo, Anna G. [D-CA-18]*	12/12/2013
Rep. Whitfield, Ed [R-KY-1]*	12/12/2013

Rep. DeGette, Diana [D-CO-1]*	12/12/2013
Rep. Blackburn, Marsha [R-TN-7]*	12/12/2013
Rep. Engel, Eliot L. [D-NY-16]*	12/12/2013
Rep. Griffith, H. Morgan [R-VA-9]*	12/12/2013
Rep. Butterfield, G. K. [D-NC-1]*	12/12/2013
Rep. Matsui, Doris O. [D-CA-6]	03/24/2014
Rep. Ellmers, Renee L. [R-NC-2]	03/24/2014
Rep. Dingell, John D. [D-MI-12]	03/24/2014
Rep. Latta, Robert E. [R-OH-5]	03/24/2014
Rep. Matheson, Jim [D-UT-4]	03/24/2014
Rep. Cassidy, Bill [R-LA-6]	03/24/2014
Rep. Yarmuth, John A. [D-KY-3]	03/24/2014
Rep. Olson, Pete [R-TX-22]	03/24/2014
Rep. Tonko, Paul [D-NY-20]	03/24/2014
Rep. Lance, Leonard [R-NJ-7]	03/24/2014
Rep. Pompeo, Mike [R-KS-4]	03/24/2014
Rep. Barrow, John [D-GA-12]	03/24/2014
Rep. Guthrie, Brett [R-KY-2]	04/28/2014
Rep. Lujan, Ben Ray [D-NM-3]	04/28/2014
Rep. Bilirakis, Gus M. [R-FL-12]	05/08/2014
Rep. Speier, Jackie [D-CA-14]	05/28/2014
Rep. Shea-Porter, Carol [D-NH-1]	05/28/2014
Rep. McMorris Rodgers, Cathy [R-WA-5]	07/09/2014
Rep. Roskam, Peter J. [R-IL-6]	07/10/2014
Rep. McCaul, Michael T. [R-TX-10]	07/15/2014
Rep. Barton, Joe [R-TX-6]	07/17/2014
Rep. Langevin, James R. [D-RI-2]	07/17/2014
Rep. McNerney, Jerry [D-CA-9]	07/22/2014
Rep. Roe, David P. [R-TN-1]	07/22/2014
Rep. Byrne, Bradley [R-AL-1]	07/22/2014
Rep. Pascrell, Bill, Jr. [D-NJ-9]	07/29/2014
Rep. Johnson, Eddie Bernice [D-TX-30]	07/30/2014
Rep. Heck, Joseph J. [R-NV-3]	09/08/2014

Rep. DesJarlais, Scott [R-TN-4] 09/09/2014
Rep. Ellison, Keith [D-MN-5] 09/11/2014
Rep. Kilmer, Derek [D-WA-6] 09/11/2014

STAAR

H.R.2285 - Strategies to Address Antimicrobial Resistance Act

Rep. Matheson, Jim [D-UT-4] (Introduced 06/06/2013)
Rep. Moran, James P. [D-VA-8] 07/23/2013
Rep. McCollum, Betty [D-MN-4] 11/20/2013
Rep. Shea-Porter, Carol [D-NH-1] 12/05/2013
Rep. Green, Gene [D-TX-29] 01/14/2014

STAAR
S.2236 - Strategies to Address Antimicrobial Resistance Act

Sen. Brown, Sherrod [D-OH] (Introduced 04/10/2014)

Other policy champions on issues relating to antibiotic resistance:

U.S. House of Representatives
Pitts (R-PA)
Shimkus (R-IL)
DeGette (D-CO)
Lance (R-NJ)

U.S. Senate
Blumenthal (D-CT)
Hatch (R-UT)
Bennett (D-CO)
Corker (R-TN)