

Public Policy Statement: Antibiotic Resistance

Antibiotics have revolutionized medicine and saved millions of lives since their introduction more than 70 years ago. Merck has played a major role in antibiotic development, extending back to the early days of antibiotic therapy, and has sustained a commitment to anti-infective R&D. The company launched one of the first antibiotics, sulfamerazine (1938), and developed the first methods for mass production of penicillin (1942). To this day, the company remains one of very few large pharmaceutical companies involved in developing new antibiotics. Our commitment has been further strengthened with the acquisition of Cubist.

Bacteria continually evolve and, as a result, bacteria resistant to virtually all available medicines are becoming more common—threatening over time our ability to treat routine illnesses and making procedures where secondary infections are common such as surgery, chemotherapy and transplantation far riskier.¹ The health and economic consequences of antibiotic resistance are “considerable and costly,” according to the World Health Organization (WHO),² making it a serious threat that demands a concerted, global response. Some estimates have ranged as high as \$20-35 billion in additional health care costs for the U.S. alone due to resistance.

Antibiotic resistance is a natural consequence and is expected with every antibiotic after a period of continued use. While the development of resistance may be able to be reduced through a number of efforts, such as responsible use of antibiotics, research must continue into newer antibiotics that are effective against multi-drug resistant bacteria.

The medical need for new antibiotics is significant and urgent. For example, at least 2 million people in the U.S. acquire serious bacterial infections each year resistant to antibiotics, and at least 23,000 people die each year due to those antibiotic-resistant infections.³ To address this growing public health issue, Merck supports policies that will ensure development of and access to a sustainable pipeline of safe and effective antibiotics, and also encourage appropriate use of the medicines to ensure their value for generations to come.

Merck’s Position on a Global Approach to Addressing Antibiotic Resistance

Addressing antibiotic resistance will require a comprehensive, global approach, including multi-sector incentives and efforts. Governments need to address challenges that limit the development of new antibiotics, and also need to ensure reimbursement for appropriate antibiotic use through strategies that recognize the diversity of national regulatory systems and specific patient circumstances. Additionally, strong, locally-driven stewardship, which considers the factors impeding appropriate use of antibiotics in different settings, is essential to slow resistance and extend the useful lifespan of these critical medicines.

¹ Similar concerns exist regarding antimicrobial agents used to treat nonbacterial infections caused by fungi, parasites or viruses, but antibacterial resistance is currently of most concern.

² *The Evolving Threat of Anti-microbial Resistance: Options for Action*, Geneva, World Health Organization, 2012. http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf. Accessed March 24, 2014.

³ Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the United States, 2013*. <http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf>. Accessed April 16, 2014.

Policies to foster development of new antibiotics

Bringing any new drug to market is a time consuming, costly and high-risk endeavor that typically takes 10 years, at an average development cost of about \$1.3 billion U.S.⁴ Even then, only one in five drugs tested in people is approved and reaches the market.⁵ For antibiotics, the economic considerations are more challenging than for many other medical areas. In addition to the unique scientific and regulatory challenges in antibiotic development, pricing and reimbursement do not reflect the true value of these life-saving drugs.⁶ As a consequence, a small minority of innovative pharmaceutical companies has maintained their R&D investment⁷ and today's antibiotic pipeline is insufficient to meet the global need.

Merck has identified several approaches that will help attract greater investment in antibiotic innovation and deliver new treatments to patients.

- **Multiple but targeted policies:** A combination of "push" (e.g., early research subsidies) and "pull" incentives (market- or value-based rewards) will be required to mobilize investment and stimulate sustainable levels of antibiotic innovation. Merck believes that these approaches should prioritize development of medicines targeting serious or life-threatening infections that cannot be treated reliably with existing medicines.
- **Development and regulatory:** Merck supports legislation and regulation to enable regulatory authorities to streamline, accelerate and defray the cost of clinical trials required for regulatory review and approval of antibiotics, and for new indications for existing antibiotics to address serious infections. We also strongly encourage the harmonization of clinical trial guidance across regulatory agencies to make registration trials both faster and more feasible.
- **Market-/Value-based incentives:** Merck believes market- and value-based approaches serve as powerful and predictable incentives for companies. We advocate for policies to ensure that antibiotic reimbursement better reflects the life-saving and societal value of antibiotics targeting serious infections. Reimbursement changes would need to be coupled with stewardship measures that ensure that patients receive the optimal treatment for their individual situations while helping manage antibiotic resistance. Merck supports efforts to reimburse antibiotics separately from bundled hospital payments based on patient diagnoses (such as the DRG in the U.S.) as a way to ensure that their use is driven only by clinical considerations, not economic considerations.

Policies to support antibiotic stewardship in human health

Antibiotic resistance occurs even with proper use of antibiotics, but widespread, inappropriate use accelerates resistance. In more developed countries, there are a number of contributing factors, such as over-the-counter sales of antibiotics, poor patient compliance, inappropriate selection of antibiotics and over prescribing. In less developed markets the situation is made worse by the prevalence of substandard medicines. Merck has identified several approaches to optimize and ensure appropriate antibiotic use in order to slow antibiotic resistance.

- **Patient outcomes vs. cost:** The primary goal of antibiotic stewardship should be to optimize clinical outcomes while minimizing unintended consequences of antibiotic use. Optimizing

⁴Tufts Center for the Study of Drug Development (CSDD) Briefing "Cost of Developing a New Drug," November 2014, Tufts CSDD and School of Medicine. http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study

⁵Michael Hay et al., "Clinical Development Success Rates for Investigational Drugs," *Nature Biotechnology* 32, (2014): 40–51.

⁶Mossialos E. et.al. *Policies and incentives for promoting innovation in antibiotic research*. The London School of Economics 2009. http://www.euro.who.int/__data/assets/pdf_file/0011/120143/E94241.pdf. Accessed June 2, 2014.

⁷Boucher H.W. (2013) 10 × '20 Progress—Development of new drugs active against Gram-negative bacilli: An update from the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 56(12), 1685 – 1694; Centers for Disease Control and Prevention. *Antibiotic Resistance Threats in the United States, 2013*. <http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf>. Accessed April 16, 2014.

clinical outcomes extends beyond any one patient getting well and may include goals such as minimizing length of stay, prevention of readmissions and reducing adverse events. Although the impetus for antibiotic stewardship programs should be patient and public health, cost savings are often the primary focus. Merck supports the development and adoption of evidence-based stewardship policies focused on patient outcomes and tailored to the setting of care, and such policies should continually be evaluated to achieve the best clinical outcomes with the lowest risk of accelerating resistance.

- **Antibiotic selection and diagnostics:**

- Diagnosics. U.S. health authorities report overuse of antibiotics in hospital patients.⁸ Merck supports use of existing tools (e.g. antibiograms) and the development of more robust technologies (e.g., rapid diagnostics) to inform prescribing and to fully realize the potential of stewardship initiatives. We support incentives for the development and uptake of rapid diagnostics that would enable evidence-based and targeted use of antibiotics across health care settings.
- Breakpoints. Setting accurate susceptibility interpretive criteria or “breakpoints” (drug concentrations where a type of bacteria is categorized as being susceptible or resistant to a particular antibiotic) is critical for individual patient care, good stewardship and the tracking of antibiotic resistance trends. Merck advocates for legislation and regulations that streamline the setting of breakpoints for new antibiotics and regular updating for all antibiotics.

- **Regulated use and quality initiatives:**

- OTC antibiotics. In many countries, antibiotics are available without a prescription or involvement of a health care professional. Merck supports policies to limit over-the-counter sales of antibiotics.⁹
- Safe, effective and quality antibiotics. Substandard medicines containing low concentrations of antibiotics may contribute to resistance. Merck believes policies to ensure the safety; effectiveness and quality of antibiotics should be established and enforced.

- **Surveillance:** Merck supports mechanisms to monitor and track resistance globally and locally in order to: monitor trends; support evidence-based decision making and responses at the individual patient and community level; and inform the development of new treatments and diagnostics.

Policies to support antibiotic stewardship in animal health

Antibiotics have an important role in ensuring the health and wellbeing of animals. Merck Animal Health supports the responsible use of antibiotics to improve and maintain the health and welfare of animals. Clinical research has shown that antibiotics, when used appropriately, are effective tools to manage disease in animal populations, protect human health by reducing the spread of zoonotic disease and are a critical component to ensuring a safe food supply. Merck develops, manufactures and markets a portfolio of antibiotics for a number of different species to support healthier animals.

- **Appropriate use:** Merck supports the responsible use of antibiotics in livestock and pets to help maintain animal health, public health and food safety. We are committed to supporting and working with veterinarians, producers and regulatory agencies to ensure that the proper, responsible and targeted use of antibiotics is managed through the appropriate channels.

⁹*The Evolving Threat of Anti-microbial Resistance: Options for Action*, Geneva, World Health Organization, 2012. http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf. Accessed March 24, 2014.

- **Alternate approaches/vaccines:** Merck Animal Health is a global leader in veterinary vaccines and continues to develop alternative approaches to the use of antibiotics, such as immunomodulation, and novel vaccines for existing and emerging animal health challenges. Merck Animal Health also conducts research to increase knowledge around antimicrobial therapy and resistance mechanisms.
- **Diagnostics:** Merck engages in improving diagnostic procedures and participates in monitoring programs to maximize the effectiveness of antibiotics and to minimize the development of resistance. Specifically, Merck supports initiatives striving to standardize and harmonize laboratory methodologies for the antibiotic susceptibility testing, establishment of breakpoints, and quantification of antimicrobial resistance.

Merck's Commitment to Advance Access to Antibiotics Globally

- Merck recognizes that antimicrobial resistance is a global concern, and we fully support the efforts by the World Health Organization and its Members to promote solutions that can respond to growing resistance across the world, including in developing countries that often face severe resource constraints.
- Through a multi-pronged strategy, Merck is improving access to medicines and vaccines by examining our approach to research and development, manufacturing and supply, registration, commercialization, and community investment.
- To guide this worldwide approach, we developed the Access to Health Statement of Guiding Principles and we strive to embed these principles into our operations and business strategies.
- In line with our overall corporate principles, Merck is committed to finding ways to make our antibiotics increasingly accessible in developed, emerging and developing markets, working in partnership with other stakeholders. We are also working with governments and other stakeholders to promote antimicrobial stewardship, including in China, India and other heavily populated countries where resistance is undermining overall population health goals.

July 2015

