

Public Policy Statement: Antimicrobial Resistance

As a pioneer in developing antibiotics, launching sulfamerazine in 1938 and penicillin in 1942, and as a global leader in developing anti-infectives for over 70 years, Merck is concerned today about the ever-increasing threat of antimicrobial resistance to global public health.

Merck promotes responsible use of antimicrobials. Merck also maintains an active program in development of anti-infectives and supports improvements in the global regulatory requirements and availability of financial incentives that will help support and accelerate the research and development of new classes of antimicrobial agents.

The introduction of antibiotics in the 1940s revolutionized medical treatment, providing effective treatment for previously deadly bacterial infections. However, bacteria tend to naturally change over time to become resistant, through mutation or exposure, to available antibiotic treatments. Indeed, widespread use of antibiotics has accelerated the problem of antimicrobial resistance globally. Today, bacterial resistance to historically effective antibiotics has become a significant public health problem¹. Similar concerns exist regarding antimicrobial agents used to treat non-bacterial infections (which include fungi and parasites).

The increasing trend in antimicrobial resistance is a source of concern as it affects future success rates of the treatment and prevention of important infections, thereby increasing the infectious risks associated with cancer treatment, organ transplantation, surgeries, and other procedures.

Solutions to the problem include efforts to slow the spread of antimicrobial resistance through effective stewardship of existing treatment, and efforts to stimulate development of new antimicrobial agents through improvements in regulatory pathways and added incentives for successful development.

Antimicrobial Stewardship

Increased use and misuse of antimicrobials in human and veterinary medicine and in agriculture have contributed to the acceleration of antimicrobial resistance. This problem has been compounded by lapses in compliance with the highest possible standards for hygiene and infection control. Merck supports and engages in activities aimed at providing more effective stewardship for existing antibiotics in an effort to slow the growth rate of resistance.

¹ Over 50 percent of healthcare-associated infections (HAIs) are caused by resistant bacterial strains. There are over 2 million cases of HAIs a year in the US, resulting in an estimated 90,000 deaths. Multidrug-resistant bacterial infections cause an estimated 25,000 deaths per year in the EU. Rates of antibiotic resistance may be much higher in the developing world. The last decade has seen the emergence of some resistant organisms for which there are no effective therapies.

Yet, effective stewardship policies that require novel antimicrobials be held in reserve for use only against the most resistant bacteria, ironically reduce the commercial value and incentives for research and development². This reduction in commercial value may be mitigated, though, by a longer period of utility for the product in a more carefully managed treatment environment.

Surveillance is an important component of antimicrobial use management. EARS-Net is a European wide network of national surveillance systems coordinated and funded by the [European Centre for Disease Prevention and Control](#) to provide European reference data on antimicrobial resistance. In the US, the Centers for Disease Control monitors antimicrobial resistance through several surveillance systems. Merck supports plans prepared by the Interagency Task Force on Antimicrobial Resistance to expand and improve existing surveillance systems³. In particular, Merck supports the goals of the National Antimicrobial Resistance Monitoring System (NARMS) Strategic Plan 2011-2015 to upgrade the tracking system and strengthen collaborative research projects, and has proposed expanding coverage of the system to include *Clostridium difficile* infection⁴.

Merck sponsors surveillance studies to track the potential for development of antimicrobial resistance to its products worldwide. The Study for Monitoring Antimicrobial Resistance Trends (SMART) has since 2002 been monitoring, globally and longitudinally, the susceptibility of intra-abdominal infections (with regard to ertapenem and imipenem) to aid in analyzing trends in antimicrobial resistance and guide therapy. Merck sponsors similar surveillance efforts to track resistance to antifungals (caspofungin and triazole).

Human Health

Development of antimicrobial resistance is natural and an inevitable consequence of treatment. While the emergence of resistance occurs by chance, dissemination of resistance occurs through selection, and selective pressure is exacerbated by exposure to antibiotics⁵. While even proper use of antibiotics can result in resistance, widespread overuse, misuse, and non-compliant use of antibiotics have contributed to acceleration in the pace at which antimicrobial resistance is developing. Lack of rapid diagnostic tools to clearly identify the bacteria causing a particular infection contributes to this problem by compelling physicians to start patients on a course of empiric therapy before they have an accurate diagnosis. Other pressures of contemporary medical practice and patient treatment expectations also contribute to overuse and misuse.

Stewardship to ensure appropriate use by health care providers and patients can slow the development of resistance and prolong the useful life of the current stock of antibiotics. Antimicrobial stewardship guidelines have been developed by a number of organizations worldwide. In the US, guidelines have been prepared by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA)⁶. A follow-up statement from the Society of Infectious

² React Facts 2007 "Decline in Antibacterial Innovation," <http://www.reactgroup.org/uploads/publications/React-publications/decline-in-antibacterial-innovation.pdf>; or Burki, 2010."Push and Pull of Antibiotic Development," The Lancet Infectious Diseases, Jan 2010:12-13.

³ Interagency Task Force on Antimicrobial Resistance. A Public Health Action Plan to Combat Antimicrobial Resistance. Fed.Reg. Vol. 76, No. 51, March 16, 2011. PhRMA comments to Docket No, CDC-2011-002D:Draft Action Plan – A Public Health Action Plan to Combat Antimicrobial Resistance; June 14, 2011.

⁴ Merck comments to Docket No. FDA-2010-N-0620: The National Antimicrobial Resistance Monitoring System Strategic Plan 2011-2015; March 25, 2011.

⁵ IOM (Institute of Medicine). 2010. *Antibiotic Resistance: Implications for Global Health and Novel Intervention Strategies*. Washington, DC. The National Academies Press. P.17.

⁶ Dellit TH, et al. "Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship." *Clin. Infect. Dis.* 2007; 44(2): 159-77. Merck distributes these guidelines to providers in a pocket version for educational purposes.

Diseases Pharmacists has been supported by IDSA and SHEA⁷. Similar guidelines have been developed by the European Society for Clinical Microbiology and Infectious Disease (ESCMID)⁸ and Therapeutic Guidelines Limited in Australia⁹.

Physicians, pharmacists, and nurses have the main responsibility for antimicrobial stewardship. Prescriber education about appropriate antimicrobial use is essential. Use of computerized physician order entry can reduce prescribing errors and ensure the right antibiotic agent is prescribed for the infection under treatment. Clinical decision support systems integrated with electronic medical records can facilitate adherence to guidelines for appropriate use of antimicrobials. Prohibition of nonprescription antibiotics may also help enforce appropriate uses, especially in developing countries.

Merck supports initiatives to promote the rational and evidence-based use of antibiotics. Merck supports the dissemination of tools for antimicrobial stewardship by distributing reprints of the 2007 IDSA/SHEA Stewardship Guidelines. Merck also prints and distributes a "pocket card" version of these guidelines that has been endorsed by IDSA, SHEA, and the Society of Infectious Diseases Pharmacists. Merck supports peer discussion programs for hospital-based health care providers where strategies to help reduce the development of resistance to antimicrobial therapy can be explored. Through these peer discussion programs, Merck helps hospitals establish procedures with the aim to shorten durations of therapy, control polypharmacy, eliminate unnecessary antibiotic use, and reduce hospital-acquired infections. Merck encourages customers to carefully target the use of Merck's antimicrobial agents to limit unnecessary exposure to antimicrobials in an effort to reduce the potential for development of antimicrobial resistance.

Globally, Merck provides a program to educate hospital personnel and help hospitals establish data collection and develop and implement protocols for appropriate antimicrobial use. Merck's program launched in India in 2009, which is endorsed by the Indian Society for Critical Care Medicine, has conducted, over the last two years, three regional workshops on antimicrobial stewardship and helped over 25 hospitals compile surveillance data and develop evidence-based antibiotic protocols. The program emphasizes the use of local microbiology data, specification of sites of infection, stratification of risk, and appropriate de-escalation of treatment.

Animal Health

Antibiotics are used both to treat infections and to prevent disease in companion animals and farm animal populations. Antibiotics are used to treat individual diseased animals, to treat herds that have high morbidity and mortality rates, and to prevent disease in herds that are at high risk of illness. Antibiotics are also used in feed for farm animals to improve the stability and balance of an animal's intestinal bacteria, improve its digestion, and, thus, its efficient use of nutrients.

In recent years, there have been widespread efforts to manage antibiotic use in animal agriculture to reduce the potential for antibiotic resistance in humans. Merck supports efforts to promote the responsible use of antibiotics in animals. Responsible use of antibiotics approved by the corresponding national and international registration authorities, like the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), is an important component of food safety – helping to keep farm animals healthy, as healthy animals are efficient producers of safe, affordable, and wholesome food.

⁷ Drew RH, et al. "Insights from the Infectious Diseases Pharmacists on Antimicrobial Stewardship guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America." *Pharmacotherapy*. 29:5 2009. 593-607.

⁸ http://www.escmid.org/escmid_library/medical_guidelines.

⁹ <http://www.tg.org.au/index.php?sectionid=41>.

Antimicrobials are approved and regulated (over the lifetime of the product) by the FDA, EMA, and other national authorities; and therapeutic antimicrobials for animal use are used under the prescription and control of a veterinarian. The approval process for antibiotics used in food animals establishes withdrawal periods from the time the last dose of antibiotic is given until the animals or products enter the food chain. These withdrawal periods ensure the safety of meat, milk and eggs from treated animals. Government programs, such as those conducted by the United States Department of Agriculture (USDA), test for antibiotic residues in food to make sure the food is safe¹⁰. Strict regulatory guidelines control the use of antibiotics in the feed of animals. Regulations govern the availability, prescription, distribution and use of these medicated feeds in food animals. Submissions to regulatory agencies for approval of antibiotics intended for animals include an environmental assessment that appraises the effects of the use of the product on flora, fauna, soil and water. When necessary, restrictions are placed on the use of these products to protect the environment.

The use of antibiotics for productivity enhancement (or "growth promotion") is controversial, especially for compounds that are listed in the World Health Organization (WHO) guidance¹¹ as medically important for human health. Merck does not market antibiotics that are listed by the World Health Organization as important for human health for productivity enhancement in food animals.

Europe deleted the growth promotion claim from its feed additive legislation in 2006. In the US, The FDA has recently been collaborating with stakeholders and has issued draft guidance¹² in an effort to increase veterinary oversight of antibiotic use in food animals and to remove growth promotion claims from compounds that are medically important in human health. Merck policy in the US is consistent with FDA's guidance. Merck does not support proposed legislation (e.g., H.R. 965 proposed by Rep. Slaughter (D-NY)) that would go beyond the FDA guidance and withdraw approval for administration of critical antimicrobial animal drugs in feed or water for therapeutic purposes that FDA considers judicious use to protect animal health and food safety¹³.

Merck will continue to work collaboratively with the national and international authorities, like FDA, EMA, WHO, and the World Organization for Animal Health (OIE); and others in the industry through the animal health associations, including the Animal Health Institute (AHI), the International Federation for Animal Health (IFAH) and IFAH-Europe on judicious antibiotic treatment in veterinary medicine.

Merck promotes with its customers adherence to guidelines on prudent use of antimicrobials developed by international and national organizations such as the World Health Organization (WHO), the World Organization for Animal Health (OIE), the World Veterinary Association (WVA), the American Veterinary Medical Association (AVMA), and the European Platform for Responsible Use of Medicines in Animals (EPRUMA).

Merck provides continuing education (CE) opportunities on responsible use of antibiotics at international, national, and local veterinary meetings. Merck sponsors and delivers to veterinarians, farmers, and feed companies, educational programs and materials on practices to ensure sustainable use of antibiotics. Merck supplies guidelines for resistance management, and provides

¹⁰ <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM124674.pdf>

¹¹ World Health Organization (WHO). Critically Important Antibiotics for Human Medicine, 3rd Edition, 2009.

¹² FDA. "Guidance on the Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals." August 2010.

¹³ Testimony of Joshua M. Sharfstein, M.D., Principle Deputy Commissioner of Food and Drugs, FDA, before the House Committee on Rules, July 13, 2009; <http://www.fda.gov/NewsEvents/Testimony/ucm171715.htm>.

educational materials on appropriate dosage and length of use of its antibiotics. An example is Merck's SLICE[®] Sustainability Project that has helped minimize the spread of resistance and enabled its anti-parasitic SLICE[®] to remain the world's leading treatment for sea lice infestation in salmon for more than a decade.

Merck engages in research efforts to increase our knowledge of the proper use of antibiotics in animals for the benefit of both human and animal health. Merck operates and participates in surveillance programs that would detect the emergence of bacterial resistance to antibiotics we market. Merck is active in research programs to develop alternative approaches to the use of antibiotics in animals, and to develop vaccines to prevent disease in companion and food animals.

Acceleration of Antibiotic Development

While the rate of development of antimicrobial resistance has been accelerating, the pace of development of new antimicrobial agents has slowed considerably during the past several decades. Only two classes of new antibacterials have come to market over the last 30 years¹⁴. The period from 1983 to 2007 saw a 75 percent decrease in systemic antibacterials approved by the FDA, reflecting a decline in the antibiotic pipeline¹⁵. A recent study of pharmaceutical company pipelines by the EMA found only 15 systemically-administered antibacterial agents with a new mechanism of action or bacterial target that might have the potential to challenge multidrug resistance – all in early phases of development¹⁶, with uncertainty whether and when any will make it to the marketplace.

The antibiotic discovery process, like drug development in general, is difficult with a high rate of failure. Antibiotic development itself requires a concerted scientific effort by a diverse group of academic and industry scientists in order to discover effective drug candidates that are not hampered by bacterial mechanisms of resistance. Basic science on antibiotics needs to be stimulated. A collaboration of industry, academia and government is needed to sustain funding for basic antibiotic research. The nature of the antibiotic market creates high costs and risks in development. Additional hurdles result from challenging regulatory requirements that inadvertently may raise the cost and risks of gaining regulatory approval of new agents, and the lack of adequate financial incentives to stimulate discovery and development.

In 2009, the Council of the European Union called on the European Commission to implement activities to promote research and development of new effective antibiotic medicines and methods; including to "...develop a comprehensive action-plan, with concrete proposals, concerning incentives to develop new effective antibiotics..."¹⁷.

A TransAtlantic Task Force on Antimicrobial Resistance (TATFAR) was created by the EU-US Summit in 2009 to develop collaboration between US and EU authorities on efforts to combat antimicrobial resistance. The Task Force is intended to improve coordination between the EU and the US on efforts to promote appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevent both healthcare- and community-associated drug-resistant infections, and develop strategies for improving the pipeline of new antimicrobial drugs. TATFAR is tasked with developing a concrete action plan to be presented to the 2011 EU-US summit.

¹⁴ EMA (European Medicines Agency) and ECDC (European Centre for Disease Prevention and Control.). (2009). *The Bacterial Challenge: Time to React*. Stockholm. P. 2

¹⁵ Spellberg B, Guidos R, Gilbert D, et al. "The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America." *Clin Infect Dis* 2008; 46:155-64.

¹⁶ EMA and ECDC. P. 17.

¹⁷ Council of the European Union. Conclusions on innovative incentives for effective antibiotics. 2009. <http://register.concilium.europa.eu/pdf/en/09/st16/st16006.en09.pdf>.

Merck supports the TATFAR initiative primarily as a way to harmonize EU, US and other regulatory guidance, and to provide greater consistency and alignment in clinical trial design and other requirements for new antibiotic approval that will streamline global development. Merck also believes TATFAR can play an important role in advancing incentives for antimicrobial development by exchanging ideas and perspectives on various approaches to this area of critical medical need.

Today Merck maintains one of the most diverse infectious disease discovery and development programs in the biopharmaceutical industry. This includes ongoing research and development programs pursuing new mechanisms of action against specific microbial targets.

Furthest in development, Merck has a monoclonal antibody in Phase II trials that shows promise in combating the effects of *Clostridium difficile* infection (CDI) a severe intestinal disease caused when *Clostridium difficile* bacteria, often acquired in a hospital setting, overrun the gut when antibiotics eradicate the normal protective intestinal flora. Merck also has a number of early-stage discovery and development programs with new antimicrobial agents.

In its animal health business, Merck promotes the use of vaccines as effective tools. Vaccinated animals are less prone to infections and therefore will require fewer antibiotics to be treated when sick.

Merck has been successful in finding new anti-infective uses for some of its existing antifungals and antiparasitics. Merck is currently evaluating the use of the existing anti-fungal NOXAFIL[®] (posaconazole) as a possible treatment for Chagas Disease, a neglected tropical disease affecting an estimated 8 million people in Latin America and for which there has been no new treatment in over 30 years. Since 1987, Merck has donated more than 2.5 billion tablets of MECTIZAN[®] (ivermectin) in more than 30 countries worldwide in an effort to eliminate river blindness, a goal WHO recently determined possible in some endemic areas in Africa. Merck has also recently launched the Hilleman Laboratories in India, a joint venture with the Wellcome Trust to develop new and improved vaccines for unmet medical needs in low-income countries.

Merck is concerned, however, that it will have difficulty maintaining this level of research and development activity without an improvement in regulatory guidance and interaction that would enable sponsors to advance antimicrobial candidates through regulatory review, and, in the absence of additional financial incentives, to offset the unique costs and market constraints on antimicrobials. Facing these challenges, a number of biopharmaceutical companies have ended their research and development in antibiotics in recent years. Today only five major biopharmaceutical companies still maintain active antibacterial discovery programs¹⁸.

Overcoming Regulatory Challenges

Regulatory data requirements for approval of antibiotics present a significant challenge. In Europe, shifting evidence standards for approval, lack of clinical trial guidelines for many indications and lack of clarity regarding the use of model-based evidence to prove safety and efficacy has discouraged some antibiotic developers.

¹⁸ Boucher HW, Talbot GH, Bradley JS, et al. "Bad Bugs, No Drugs, No ESKAPE! An Update from the Infectious Diseases Society of America." *Clin Inf Dis*. 2009;48:1-12.

The Council of the European Union in 2009 called upon the European Commission to "identify appropriate regulatory instruments to facilitate early approval for new antibiotics...including strategies for adequate post-authorization follow-up."¹⁹ Advocates in Europe have proposed allowing conditional approval of antibiotics on the basis of limited clinical data and a deferral of some phase III studies as post-approval commitments by the sponsor.

In the US, the FDA expects the efficacy of new antibiotics to be based on comparison to an existing antibiotic, through an active-control, non-inferiority trial design. For some indications (such as acute bacterial otitis media, acute bacterial sinusitis, and acute bacterial exacerbation of chronic bronchitis), the Agency recommends demonstration of superiority over placebo in randomized clinical trials. However, significant ethical issues may arise when considering placebo-controlled design for these bacterial infections. Trial designs that demonstrate superiority to a substandard treatment are clearly unethical. To avoid substandard treatment, patients treated in clinical trials comparing an existing with a new antibiotic must be infected with bacterial strains that have not become resistant. Therefore, by design, new antibiotics are not demonstrating efficacy against resistant bacteria. There is no clear regulatory pathway/guidance facilitating the study of such resistant organisms, considering that the current regulatory paradigm demands large clinical trials, which are difficult-to-impossible to enroll in a reasonable amount of time and, thus, are discouraging sponsors from initiating such development programs.

Recent draft guidance documents issued by the FDA on antibiotic clinical trial design²⁰, while a welcome development, have generated concern among manufacturers, who view them as raising the requirements for approval (and, therefore, development costs, including the costs of clinical trials)²¹. The adoption of the FDA's most recent draft guidances could prevent the development of new antibacterial agents for some of the most treatment-resistant indications²².

Regulatory guidance should encourage feasible and informative clinical trial design. Merck recommends that the FDA reconsider these provisions to ensure a proper balance between scrutability and practicality.

¹⁹ Council on the European Union. Page 5.

²⁰ Draft guidance issued in recent years include guidance on developing antimicrobial drugs for treatment of: acute bacterial sinusitis (2007), acute bacterial otitis media (2008), acute bacterial exacerbation of chronic bronchitis in patients with COPD (2008), community-acquired bacterial pneumonia (2009), hospital-acquired bacterial pneumonia (2009), and ventilator-associated bacterial pneumonia (2009). Additional FDA guidance include: use of non-inferiority studies to support approval of antibacterial drug products (drafted 2007 and finalized 2010), and non-inferiority clinical trials (2010).

²¹ See PhRMA comments to Docket No, CDC-2011-002D: Draft Action Plan – A Public Health Action Plan to Combat Antimicrobial Resistance; June 14, 2011.

²² Comments submitted by PhRMA to the FDA on behalf of the industry can be found at the following links:

- Acute bacterial otitis media (2008), Docket #: 2008N-0004 <http://www.regulations.gov/#!documentDetail;D=FDA-2008-N-0041-0005>
- Acute bacterial exacerbation of chronic bronchitis in patients with COPD (2008), Docket #: FDA-2008-D-0419 <http://www.regulations.gov/#!documentDetail;D=FDA-2008-D-0419-0006>
- Community-acquired bacterial pneumonia (2009), Docket #: FDA-2009-D-0136 <http://www.regulations.gov/#!documentDetail;D=FDA-2009-D-0136-0007>
- Hospital-acquired bacterial pneumonia and Ventilator-associated bacterial pneumonia (2009), Docket #: FDA-2010-D0589. <http://www.regulations.gov/#!documentDetail;D=FDA-2010-D-0589-0008>
- Non-inferiority clinical trials (2010), Docket #: FDA-2010-D-0075. <http://www.regulations.gov/#!documentDetail;D=FDA-2010-D-0075-0018>

Improving Incentives for Discovery and Development

The market for antibiotics does not provide the incentives that are typical for other types of drugs. Brand prices for novel antibiotics are comparatively low and antibiotic regimens are primarily a one-time, 5-10 day course of therapy. After regulatory approval, most novel antibiotics are reserved for use when a patient fails or identified bacteria are resistant to current therapies. As such, the expected return on companies' R&D investment is very low and may not even offset the costs of development.

Given the complexity of the discovery and development process, the hurdles involved in bringing a new antibiotic successfully to market, and the limited return possible on the investment, new incentives for manufacturers are needed to encourage an increased front-end investment in basic science and discovery and a greater willingness to fund the expensive and challenging process of completing clinical trials, gaining regulatory approval and establishing market access.

A mixture of "push" incentives (early research subsidies) and "pull" incentives (outcome-based rewards) will be required to fill the current gaps and stimulate a growing pipeline of antibiotics addressing the future challenges. As detailed by the London School of Economics in a study for the Swedish Presidency of the Council of the European Union, push incentives could include financial support to spur development in the form of capacity-building grants, research tax credits, funding for translational research, funding for open access data repositories such as molecule libraries, and cooperative agreements with government. Pull incentives could include efforts to increase the return on investment through exclusivity extensions, innovative pricing models, advance market commitments, risk-sharing reimbursement arrangements, and monetary prizes²³.

Merck supports legislation that would increase the incentives for antibiotic research and development. An example in the US is legislation introduced in the House of Representatives (HR 2182 - the Generating Antibiotic Incentives Now (GAIN) Act) that would provide intellectual property incentives aimed at spurring investment in antibiotic research and development.

Conclusion

The imperative to develop new generations of antibiotics is critical but the obstacles are substantial. It is time for governments to implement the right mix of reduced and realistic regulatory framework and enhanced financial incentives to encourage significant increases in private-sector investment in antibiotic research and development, in order to stay ahead of the imminent public health dilemma from expanding antimicrobial resistance.

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²³ Morel CM, Mossialos E. Stoking the antibiotic pipeline. BMJ 2010;340:1115-18.
http://www.bmj.com/cgi/section_pdf/340/may18_2/c2115.pdf