Pfizer Policy Position on Antimicrobial Resistance

The world faces a large and growing problem due to infections caused by bacterial pathogens that are resistant to antibiotics. Minor infections can become serious and even fatal when these pathogens are involved. Other medical interventions that depend on antibiotics, such as surgery and transplants, are becoming more risky and may become more difficult in the future due to the dwindling supply of new antibiotics. The Davos Declaration signed by more than 100 companies and trade associations in January 2016, called for collective action to create a sustainable and predictable market for antibiotics, vaccines and diagnostics, that encourages appropriate use for new and existing treatments. As one of the original signatory companies of the Davos Declaration, Pfizer has joined other pharmaceutical companies in endorsing the Industry Roadmap for Progress on Combating Antimicrobial Resistance. In addition, as many factors contribute to pathogen resistance, Pfizer endorses a four-part strategy to help address this issue: stewardship, surveillance, vaccination, and R&D incentives. Antimicrobial stewardship practices can help to reduce the spread of antimicrobial resistance (AMR) by applying greater oversight of antibiotic usage and enabling more rational and judicious prescribing practices, and supporting responsible manufacturing practices. Regional and global surveillance of antibiotic resistance patterns are an important tool to assess both the nature and the scope of the problems as well as the effectiveness of our efforts to combat them. Vaccines serve as a significant tool to prevent infection and therefore decrease the use of antimicrobial drugs. Renewed Focus on antimicrobial R&D efforts and supporting the development of additional antimicrobials and vaccines will be critical in broadening the tools available to address antimicrobial resistance. Pfizer believes that that the speed and the scope of R&D can be incentivized through a mix of economic incentives and regulatory reforms.

Background
Antibiotic resistance is a global problem. Unlike almost every other class of drug, antibiotics drive their own obsolescence by selecting antibiotic-resistant bacteria. Infections caused by antibiotic-resistant bacteria extract a significant public health and economic burden on healthcare systems.

An industry Declaration on Antimicrobial Resistance was announced at the World Economic Forum in Davos, Switzerland on January 20th 2016. Pfizer along with over 100 companies and industry trade associations, from 18 different countries, signed the declaration. The Davos Declaration called for collective action to create a sustainable and predictable market for antibiotics, vaccines and point – of –care diagnostics, which encourages appropriate use of new and existing treatments. It also called for coordinated action to improve infection prevention, hygiene, stewardship, and conservation measures.

The pharmaceutical industry recognizes our responsibility and remains committed to playing a significant part in this long-term effort. Given the unique scientific, economic, public health and environmental challenges presented by AMR, collaboration between stakeholders is essential to maximize progress. Pfizer along with other pharmaceutical companies have developed the Industry Roadmap for Progress on Combating Antimicrobial Resistance.

There are now several high profile efforts to address AMR globally. In the US, the Presidential Advisory Council on Combating Antibiotic – Resistant Bacteria (PAC-CARB) was established in March 2015. The role of PAC-CARB is to help develop and implement the National Strategy for Combating Antibiotic-Resistant Bacteria and the National Action Plan for Combating Antibiotic-Resistant Bacteria.

In addition, the G7 countries released a Declaration on addressing antibiotic resistance at the G7 Health Ministers meeting in Berlin in October 2015. In 2011 countries in the WHO South-East Asia Region signed a declaration on antimicrobial resistance in Jaipur to prioritize action against antibiotic resistance. During the Sixty-eighth World Health Assembly in May 2015, the WHO released the Global Action Plan on Antibiotic Resistance. The Pan American Health Organization (PAHO) is also leading a regional response and will provide technical support to member countries in addressing the strategic objectives derived from the WHO global action plan on AMR. More recently, the G7, G7 Health Ministers, and the G20 have released follow up statements in support of the global efforts to combat AMR.

A report on antibiotic research, commissioned by the Swedish Government and issued by the London School of Economics and Political Science (LSEPS), makes a broad recommendation for governments to create new incentives to promote the research and development of antibiotics in light of the growing concern over resistance to existing first line antibiotics. The LSEPS report differentiates current R&D incentives into two primary types – push and pull, and the need for additional pull incentives.
Push incentives focus on removing barriers to the developer, largely by decreasing the costs for investments in R&D. These incentives tend to impact the earlier stages of the development process, and include R&D tax credits and grants.

Pull incentives involve the commitment of financial reward after a technology has been developed, and include intellectual property extensions, advanced marketing commitments, monetary prizes, and market entry rewards.

Regulatory incentives include approaches to accelerated assessment and approvals, such as the Generating Antibiotic Incentives Now (GAIN) Act, the Limited Patient Antibiotic Drug Act (LPAD), and 21st Century Cures.

A recent report entitled, *Securing New Drugs for Future Generations: The Pipeline of Antibiotics* published in May 2015 made similar recommendations including the focus on innovation prizes. That report also focused on the need to de-couple antibiotic market entry from usual market-driven incentives, based upon use of the product in order to protect against over-prescribing.

**Key Facts and Figures**

- According to the World Bank the negative impact of AMR on total global gross domestic product (GDP) in 2050 is between 1.1% and 3.8%.10
- In the United States, AMR bacteria cause at least 2 million infections each year. CDC estimates that 23,000 people die each year as a direct result of these infections.11 Many more people die from other conditions that are complicated by an antibiotic-resistant infection.
- The National Action Plan for Combating Antibiotic-Resistant Bacteria states that stewardship practices could prevent 619,000 infections and 37,000 deaths from antibiotic-resistant bacteria in the US over the next five years.12
- Anti-microbial resistant infections cause over 50,000 deaths annually in Europe; hundreds of thousands more die in other regions.13
- The economic burden created by antibiotic resistance in the United States is estimated at $55bn ($20bn in health service costs and $35bn in lost productivity) per year.14
- In the EU, Iceland and Norway, the burden of additional hospital care due to AMR infections was estimated to be approximately €1.6bn in 2012.15
- In India, 57% of the infections caused by *Klebsiella pneumoniae*, a dangerous superbug, were found to be resistant to one type of last-resort drug in 2014, an increase of 29% in 2008.16
- Based on studies by KPMG and RAND Europe, a continued increase in resistance would reduce world GDP by 2-3.5% by 2050.17
- In the EU, the economic burden associated with antibiotic resistant infections is estimated to be about €1.5 billion per year.18
- A US study found the mean cost per patient for hospitals treating methicillin-resistant *Staphylococcus aureus* (MRSA infections) is up to 40% greater than the cost for treating methicillin-sensitive *Staphylococcus aureus* (MSSA).19

**Pfizer’s Position: Davos Declaration and the Industry Roadmap for Progress**

As a leading company supporting the Davos Declaration, Pfizer welcomes the continued focus on AMR, as well as regional and international debate. This work has established a comprehensive agenda and challenges each key stakeholder group to act and contribute to managing the threat of resistance. As a part of the Industry Roadmap for Progress on Combating Antimicrobial Resistance, there are four key commitments on which the undersigning companies of this document will deliver:

1. Reduce the environmental impact from the production of antibiotics, including a review of the companies’ manufacturing and supply chains, and working with stakeholders to establish a common framework for assessing and managing antibiotic discharge.
2. Play an important role ensuring antibiotics are only used by patients who need them, through continued doctor and patient education, examination of the companies’ promotional activities, sharing of surveillance data with public health bodies and healthcare professionals, and collaboration with stakeholders to reduce uncontrolled antibiotic purchase.
3. Explore new opportunities for open collaborations between industry and the public sector to address challenges in the research and development of new antibiotics, vaccines and diagnostics, recognizing the value these bring to society.

4. For both existing and future antibiotics and vaccines, improved access is essential, and must be balanced with health system measures to ensure appropriate use. We support mechanisms to facilitate affordable access to high quality new and existing antibiotics, diagnostics and vaccines to the patients who need them, in all parts of the world and at all levels of income. We recognize the success of programs to improve global access to vaccines and drugs in HIV, TB, and malaria.

**Pfizer’s Position: Antimicrobial Stewardship**

Proper management of antibiotic use requires an evidence-based approach, prescriptively applied to discrete health care settings, as well as the individual patient’s situation. Thus, it is necessary for infectious disease specialists, microbiologists, clinical pharmacists and other key caregivers to work together as a team. Pfizer believes that multiple strategies aimed at improving the appropriate use of anti-infectives should be employed at health care institutions and endorses strategies that ensure patient access to the medicines that treat serious infections. Pfizer and other pharmaceutical companies have developed and endorsed antibiotic stewardship strategies through the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). More details can be found on the IFPMA website at: [http://www.ifpma.org/innovation/anti-microbial-resistance.html](http://www.ifpma.org/innovation/anti-microbial-resistance.html). Pfizer routinely sponsors and conducts medical education outreach to healthcare providers through a variety of mechanisms, including medical symposia and Pfizer sponsored preceptorships, to ensure appropriate utilization of antibiotics and improve infection prevention and control.

Pfizer recently partnered with the British Society for Antimicrobial Chemotherapy (BSAC) and the University of Dundee to launch the Massive Open Online Course (MOOC) on antimicrobial stewardship. The course helps health care professionals understand and address the global threat of antimicrobial resistance, focusing on how to responsibly use high-quality antibiotics safely in everyday practice. Over 5,000 healthcare professionals had completed the course, with over 15,000 registrants. Pfizer currently provides support to BSAC for translation of the MOOC into Chinese and other languages to enable broader global access to antimicrobial stewardship (AMS) training.

Effective stewardship of antibiotics also includes responsible manufacturing practices. Pfizer supports measures to reduce environmental impact from production of antibiotics, and will:

1. Review our own manufacturing and supply chains to assess good practice in controlling releases of antibiotics into the environment.
2. Establish a common framework for managing antibiotic discharge, building on existing work such as Pharmaceutical Supply Chain Initiative (PSCI), and start to apply it across our own manufacturing and supply chain by 2018.
3. Work with stakeholders to develop a practical mechanism to transparently demonstrate that our supply chains meet the standards in the framework.

**Pfizer’s Position: AMR Surveillance**

Regional and global surveillance of antibiotic resistance patterns provides physicians with important information to help them choose the most effective antibiotics and to plan and assess stewardship and strategies. Pfizer sponsors the most comprehensive global antimicrobial resistance surveillance program in the Industry. These programs provide critical data regarding antibiotic resistance patterns that, in turn, enable physicians and healthcare providers to make the most appropriate treatment choices for their patients. Historically Pfizer has supported several surveillance programs including:

1. The LEADER (Linezolid Efficacy and Accurate Determination of Resistance) program, established in 2004, is a national (US) initiative to monitor the activity of linezolid and comparator agents against target Gram-positive pathogens.
2. The ZAAPS (Zyvox Annual Appraisal of Potency and Spectrum) program has surveyed and documented the spectrum and activity of linezolid tested against non-USA Gram-positive pathogens for nine consecutive years (2004–12).
3. The SENTRY Antimicrobial Surveillance Program, which began in 1997 and is managed by JMI Laboratories, was designed to monitor the predominant pathogens and antimicrobial resistance for both nosocomial and community-acquired infections globally. Each year, the program surveys over 30,000 Gram-positive and Gram-negative organisms from medical centers participating in the global study.

4. The TEST (Tigecycline Evaluation and Surveillance Trial) program was established in 2004 and is a global program that tracks antibiotic resistance for both Zvyox and Tygacil antibiotics as well as other antibiotics. The scope of the TEST program (2004-2016) has reached 2,700 sites in 69 countries (cumulative total) since its inception. Currently, the program holds 200 active sites in 52 countries. Since 2004, the TEST program has provided valuable data and information – generating over 360 posters and 57 peer reviewed manuscripts to date. Results are available on a web-based interactive platform that includes a dynamic database of “real-time” surveillance data

These programs have provided data to enable physicians to make the most appropriate antibiotic choices for their patients. As of today, Pfizer surveillance programs have generated data in 69 countries and since 2004, have served as the primary sources for 128 scientific papers.

In 2017, Pfizer will continue to expand its leadership position in antibiotic surveillance and stewardship through several initiatives. Pfizer is a partner in the DRIVE-AB initiative, a public-private partnership/consortium that is funded by the European Innovative Medicines Initiative (IMI). The consortium includes activities in antibiotic use and stewardship, new economic models for antibiotic use, and management and communication.

The goal of the Global Antifungal Surveillance Program is to determine the frequency of occurrence of resistance among fungal pathogens causing infections in hospitalized patients. This global program includes 62 participating medical centers in the SENTRY Program, located in North America, Latin America, Europe, and the Asia-Pacific region.

Pfizer also provides support for two China-based antibiotic resistance surveillance programs:

1. Since 2005, CHINET has investigated the anti-bacterial resistance and susceptibility rate of clinical isolates from major regions in China.
   a. Its 10-year report was just published, indicating the increased carbapenem resistance and the reduced MRSA incidence in China.
   b. It has accumulated around 600,000 isolates so far and will also expand it coverage to all regions within in 2017.

2. CHIFNET investigates the anti-fungal resistance and susceptibility rate from all the regions since 2009, with about 3,500 isolated collected.

**Pfizer’s Position: Vaccines and AMR**

In addition to the rational use of antimicrobial drugs, Pfizer believes that vaccines are essential tools in our fight against antibiotic resistant infections. Vaccines not only protect the vaccinated individual by direct immunization but also can protect others through indirect immunization (assuming the overall vaccination rate is high enough). In addition vaccines can also reduce disease caused by antimicrobial-resistant strains. It has been reported that the pneumococcal conjugate vaccine not only reduces the incidence of invasive antibiotic-resistant pneumococcal infections in young children receiving the vaccine, but it also reduces transmission of these strains to their younger siblings and to adults. In a recent study done by the CDC, an examination of U.S. pneumococcal bacteria from surveillance sites across the United States demonstrated a decrease of multidrug – resistance in the strains covered by the vaccine in pediatric populations (<5 years). The study specifically showed that there was a 93% and 86% reduction of isolates that were resistant to either single or multiple antibiotics, respectively. In separate recent analysis vaccine effectiveness using CDC data in the 35 years population of age by Suaya, et al., the incidence of invasive pneumococcal disease (IPD) caused by an antibiotic – resistant strain of pneumococcal bacteria decreased by up to 67% for three consecutive epidemiological years from 2010 to 2013.

The CDC now advocates this concept that developing new vaccines can decrease rates of antibiotic-resistant infections. A report titled, Role of Vaccination in Reducing Antimicrobial Resistance, was published by Vaccines Europe in 2013. It cites evidence supporting the preventive use of antibacterial vaccines to protect individuals and communities against infectious disease, including those caused by resistant bacterial strains.
The use of vaccines in routine national immunization programs along with the rational use of antimicrobials can produce synergistic gains in public health. By reducing the incidence of infections, vaccines can extend the clinical utility of antimicrobials. Fewer infections translate to fewer prescriptions for these drugs, and thus reduces the risk of antimicrobial resistance. We thus agree with the call for national immunization plans that ensure access to vaccinations for citizens of all ages that can benefit from them, as outlined by Vaccines Europe (2013).

Pfizer has made significant and substantial investments in vaccine R&D to develop new vaccines and to support several vaccines already in clinical usage.

**Pfizer’s Position: New Infectious Disease R&D Incentives**

There have been recent proposals in the US and EU that examines push-pull models as a means to significantly improve the incentives to pursue new product development. The Report to the President on Combating Antibiotic Resistance, based on recommendations of the U.S. President's Council of Advisors on Science and Technology (PCAST), was submitted in September 2014. The report makes eight recommendations including modernization of clinical trials, antimicrobial stewardship and infection surveillance, more funding for basic research, international cooperation, and restrictions on use of antibiotics in agriculture. Also singled out in the report was the essential need to incentivize new R&D.

In 2012, the Generating Antibiotic Incentives Now (GAIN) Act was enacted into US law. The GAIN Act provides pharmaceutical companies with incentives to develop new antibiotics to combat the growing problem of antibiotic resistance. One of the GAIN Act’s key provisions is that it provides five years of additional exclusivity to qualified infectious disease products (QIDP) at the time of their entry into the market. This five year exclusivity is in addition to existing exclusivity. The GAIN Act also adds an additional six months of exclusivity for approved antibiotics that have been paired with a companion diagnostic test. Under GAIN, 58 antibacterial drug candidates, representing 13 different antibacterial drug classes including nine new compounds not currently used in humans, have been granted QIDP status and are currently in development, with six new antibacterials approved as of January 2016.

Pfizer believes that a mix of different and complementary incentives is needed to encourage increased AMR-focused antibiotic and vaccine development within the framework of the regulatory and IP systems applicable to the particular jurisdiction.

- **Novel Intellectual Property Mechanisms:** A transferable regulatory data/marketing exclusivity or IP extension for the development of an antibiotic drug that in turn could be applied to a different drug in that company’s portfolio and could create meaningful incentives for antibiotic and vaccine development. Such incentives could be designed to be both equitable for governments and society, while providing a reasonable return for private enterprises and new antibiotics for society. In the EU the equivalent of GAIN incentives (additional 5 years’ regulatory exclusivity or IP protection for the product itself) may be useful as well as one year of exclusivity transferable to another product.

- **Transferable Priority Review Vouchers (tPRV):** In the US the tPRV provides the option to transfer a priority review to a higher value asset; these have been used successfully in the United States. Since transferable priority review vouchers can be exchanged or “sold” between companies, this feature creates a strong incentive. tPRVs should be supported by the US legislature because of the potential positive impact on antibiotics R&D.

- **R&D Tax Credits:** Tax credits have appeal as they can help to significantly decrease the financial burden of R&D. They have been successfully used as part of the Orphan Drug Act, so are already proven incentives.

- **Regulatory Flexibility:** Acceptance of innovative clinical trial protocols and a willingness to run trials with evidence that recognizes the unique characteristics of antibiotics and how they work (e.g. greater use of pool microbiological data across body sites, augmenting that with non-clinical susceptibility and pharmacokinetic (PK) data) is needed.

- **Diagnostics:** Regulatory and economic incentives should also include the development of diagnostic assays, which can differentiate antibiotic-resistant from antibiotic-sensitive strains of bacteria, and will be a key enabler for the development and usage of targeted, new generation antibiotics.

Active discussions are currently underway in the US and EU on how regulatory changes envisioned by the GAIN Act in the US would be applied to the European regulatory system. This could include the automatic acceptability of new antibiotic drug and vaccines into EU accelerated regulatory schemes (PRIME and Adaptive Pathways).

One other incentive that has recently been raised is a “pay or play” levy proposed by The Review on Antimicrobial Resistance, which would tax companies not involved in anti-infective R&D. We do not believe this is the right solution.
Taxes can add significant inefficiencies including, in this case, attracting less qualified companies to the area and unfairly targeting biopharma companies for a broad, complex challenge that involves all of the health care system. In addition, there is real potential for such a tax to shift R&D resources away from other critical public health needs.

Pfizer believes that we should be working with industry partners, healthcare providers and governments towards incentives that support additional investment and innovation in this critical challenge in ways that work synergistically within the global healthcare environment.

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