

PRESIDENTIAL ADVISORY COUNCIL ON  
COMBATING ANTIBIOTIC-RESISTANT BACTERIA

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**Meeting Summary**

PACCARB Inaugural Public Meeting  
September 29, 2015

Department of Health and Human Services  
Great Hall, Hubert H. Humphrey Building  
200 Independence Avenue, SW  
Washington, DC 20201

9:00 AM – 5:00 PM ET

## Table of Contents

Welcome and Background.....	1
Message from the Chair and Co-Chair .....	2
Council Member Introductions .....	2
Keynote: John P. Holdren, Director, White House Office of Science and Technology Policy .....	2
Remarks from the United States Department of Agriculture .....	5
Remarks from the Department of Defense .....	6
Remarks from HHS.....	7
A Healthier Nation: Combating Antibiotic-Resistance .....	7
Interagency Panel Discussions: National Strategy and Action Plans for Combating Antibiotic-Resistant Bacteria Agency Updates .....	8
Goal 1: Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections .....	8
Goal 2: Strengthen National One-Health Surveillance Efforts to Combat Resistance .....	13
Goal 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria.....	17
Goal 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines.....	19
Goal 5: Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development .....	24
Public Comments .....	28
Next Steps and Adjournment .....	31
Appendix A: Charter: Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria .....	32
Appendix B: Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) Member Roll-Call, September 29, 2015.....	38
Appendix C: Roster, Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria .....	40
Glossary of Abbreviations .....	42

# PRESIDENTIAL ADVISORY COUNCIL ON COMBATING ANTIBIOTIC-RESISTANT BACTERIA

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## Welcome and Background

Bruce G. Gellin, M.D., M.P.H., designated federal official for the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), called the meeting to order at 9:02 a.m., welcoming the Council members, federal representatives, and all those interested in the global problem of antibiotic resistance. The meeting was webcast. All PACCARB resources and information are available online at <http://www.hhs.gov/ash/carb/index.html>.

On September 18, 2014, President Barack Obama signed Executive Order 13676 stating the following:

The discovery of antibiotics in the early 20th century fundamentally transformed human and veterinary medicine. Antibiotics save millions of lives each year in the United States and around the world. The rise of antibiotic-resistant bacteria, however, represents a serious threat to public health and the economy. The Centers for Disease Control and Prevention (CDC) in the Department of Health and Human Services (HHS) estimates that annually at least two million illnesses and 23,000 deaths are caused by antibiotic-resistant bacteria in the United States alone.

Detecting, preventing, and controlling antibiotic resistance requires a strategic, coordinated, and sustained effort. It also depends on the engagement of governments, academia, industry, healthcare providers, the general public, and the agricultural community, as well as international partners.

The Executive Order established this Advisory Council to provide advice, information, and recommendations to the Secretary regarding programs and policies for nine areas. Dr. Gellin said these nine areas constitute the charge to the Council:

- Preserve the effectiveness of antibiotics by optimizing their use.
- Advance research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship.
- Strengthen surveillance of antibiotic-resistant bacterial infections.
- Prevent the transmission of antibiotic-resistant bacterial infections.
- Advance the development of rapid point-of-care and agricultural diagnostics.
- Further research on new treatments for bacterial infections.
- Develop alternatives to antibiotics for agricultural purposes.
- Maximize the dissemination of up-to-date information on the appropriate and proper use of antibiotics to the general public and human and animal healthcare providers.
- Improve international coordination of efforts to combat antibiotic resistance.

Appointments to the Council reflect an attempt to gather a wide range of expertise and perspectives from fields such as human and animal health care, public health, agriculture, and biology. As a federal advisory committee, the group is subject to the guidelines of the Federal Advisory Committee Act, including disclosure of potential or apparent conflicts of interest. (For more details, see [www.gsa.gov/faca](http://www.gsa.gov/faca).)

The Council members were sworn in by Acting Assistant Secretary for Health Karen B. DeSalvo, M.D., M.P.H., M.Sc., at an administrative session on Monday, September 28, 2015. Dr. Gellin thanked all the HHS staff working behind the scenes to coordinate this inaugural meeting of the PACCARB. (The PACCARB charter is in Appendix A.)

### **Message from the Chair and Co-Chair**

Martin J. Blaser, M.D., Chair, welcomed the audience and panelists for this meeting. He congratulated those selected to serve on this important group at a historical moment. Dr. Blaser said there is an opportunity to tackle a problem that is already big and threatens to become much worse unless something can be done. The goal of the public meeting was to hear from federal colleagues about what their agencies are doing about this problem.

Vice Chair Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, also welcomed the members, panelists, audience, and those joining online. He said it is a pleasure to work with Dr. Blaser and the Council on this important topic.

### **Council Member Introductions**

Members of the Council introduced themselves and briefly described their backgrounds and experience. (A list of present voting and nonvoting members appears in Appendix B. The full roster is in Appendix C. Member biographies are available at <http://www.hhs.gov/ash/carb/membership/index.html>.)

### **Keynote**

#### **John P. Holdren, Director, White House Office of Science and Technology Policy (OSTP)**

Dr. Holdren thanked the Council members on behalf of President Obama for agreeing to serve in this important role. Antibiotics have been an immensely important part of public health since the discovery of penicillin in 1928. The surge in antibiotic resistance has undermined the ability of health care providers to perform a range of procedures, such as organ transplants. It is likewise a threat to animal health and is an important concern for the food supply.

In September 2014, three key documents emerged. First, the President's Council of Advisors on Science and Technology (PCAST), co-chaired by Dr. Holdren, delivered its report to the President, [Combating Antibiotic Resistance](#), which included recommendations for federal government actions. The White House subsequently released the [National Strategy for Combating Antibiotic-Resistant Bacteria](#), which articulated national goals, priorities, and specific objectives to provide a framework for federal investments and efforts. Finally, President Obama signed Executive Order 13676, [Combating Antibiotic-Resistant Bacteria](#), which states:

The Federal Government will work domestically and internationally to detect, prevent, and control illness and death related to antibiotic-resistant infections by implementing

measures that reduce the emergence and spread of antibiotic-resistant bacteria and help ensure the continued availability of effective therapeutics for the treatment of bacterial infections.

In addition to establishing PACCARB, the Executive Order created a federal interagency task force to facilitate and monitor implementation of the Executive Order and the National Strategy. Notably, Dr. Holdren said, the Executive Order directed the task force to “submit a 5-Year National Action Plan to the President that outlines specific actions to be taken to implement the Strategy. The Action Plan shall include goals, milestones, and metrics for measuring progress, as well as associated timelines for implementation.”

The [National Action Plan](#) was released March 27, 2015. It establishes five goals for combating antibiotic-resistant bacteria:

1. Slow the emergence of resistant bacteria and prevent the spread of resistant infections.
2. Strengthen national One-Health surveillance efforts to combat resistance.
3. Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.
4. Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.
5. Improve international collaboration and capacities for antibiotic resistance prevention, surveillance, control and antibiotic research and development.

Dr. Holdren said combating antibiotic-resistant bacteria is among the most complex and consequential challenges facing the United States and the world. The complexity lies in the fact that the problem has multiple drivers, many of which are still poorly understood. Identifying them requires multidisciplinary expertise around emerging antibiotic resistance, including understanding the interaction of genetic and environmental factors. The diversity of the PACCARB reflects the need for an interdisciplinary approach.

In June, the [White House Forum on Antibiotic Stewardship](#) brought together stakeholders from food companies, retailers, and animal and human health advocacy to promote optimal use of antibiotics. Many of the participants have been pushing for years or even decades for more judicious use of antibiotics. Participants shared their specific commitments to change over the next 5 years to slow the emergence of resistant bacteria and prevent the spread of resistant infections. Dr. Holdren said the commitments underscore the need for broad community involvement. They also demonstrate the power of voluntary action to effect sweeping changes. Many food producers are already taking steps to phase out the use of medically important antibiotics for growth production in livestock, said Dr. Holdren.

The Executive Order stipulates that within 180 days of the release of the National Action Plan and annually thereafter, the federal interagency task force will update the President on federal actions to combat antibiotic-resistant bacteria, describing progress on the implementation of the National Action Plan and the National Strategy. It will also identify barriers to implementation and offer recommendations for new or modified actions. To date the following progress has been reported:

**Goal 1: Slow the emergence of resistant bacteria and prevent the spread of resistant infections.**

The U.S. government (USG) published new guidelines, [Core Elements of Antibiotic Stewardship for Nursing Homes](#). The Centers for Medicare and Medicaid Services (CMS) published a proposed rule that would require all long-term care facilities that participate in Medicare or Medicaid programs to update infection control and prevention programs and implement antibiotic stewardship programs. Animal health efforts have focused on ending the use of medically important antibiotics for growth promotion in livestock. The Food and Drug Administration (FDA) finalized the Veterinary Feed Directive (VFD), which requires antimicrobials to be used for animal health only under the direction of a veterinarian. The White House Forum on Antibiotic Stewardship highlighted commitments from stakeholders to slow the emergence of antibiotic resistance.

**Goal 2: Strengthen national One-Health surveillance efforts to combat resistance.**

The USG brought more laboratories online to improve detection and surveillance of emerging infections; the laboratories are the first members of a communication network that will report trends to public health authorities. Initial steps have been taken on work that will be used by academia, manufacturers, and pharmaceutical companies to design the next generation of diagnostic tests and therapeutics. In animal health, testing of retail meat for the presence of antibiotic-resistant bacteria has doubled to better inform decision-making on antibiotic trends. To collect more information, FDA published a rule that proposes additional reporting requirements for the use of antibiotics approved in food producing animals.

**Goal 3: Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.**

The USG has provided \$11 million in first-year funding for projects on rapid detection. Also, HHS is continuing efforts to support development of novel diagnostic platform technology that identify antibiotic resistance in patient samples, reducing delays in appropriate treatment. CMS and FDA are working to ensure that a regulatory pathway is in place when novel diagnostics are ready for widespread use.

**Goal 4: Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.**

The need to bolster the pipeline is important. Only a small proportion of the vaccines and therapeutics in development now address antibiotic-resistant bacteria. At least one is expected to be approved soon.

**Goal 5: Improve international collaboration and capacities for antibiotic resistance prevention, surveillance, control and antibiotic research and development.**

Among the remarkable progress internationally, the USG worked with international partners to pass the World Health Organization's (WHO's) Global Action Plan for Antimicrobial Resistance, including the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE). The USG worked with 14 partner countries to develop milestones under the Global Health Security Agenda (GHS) and is committed to the [GHS Antimicrobial Resistance Action Package](#). International meetings in the planning stages include a workshop in China on drug residue monitoring and antibiotic use in agriculture and

planning a meeting with the European Union to harmonize definitions to enhance international communication.

Dr. Holdren concluded that the USG is clearly making progress, but a lot of work remains. Secretary Sylvia Mathews Burwell and President Obama are relying on PACCARB to ensure that the federal government stays focused and accountable and can overcome challenges.

### **Council Member Questions & Answers (Q&A)**

Dr. Blaser asked what major challenges pose obstacles to achieving the goals of the National Action Plan. Dr. Holdren responded that the challenges are the same as those for any initiative that aims to create substantial change. For example, those who are doing well under the status quo are reluctant to change. There is a need to educate people about the magnitude of the threat and the feasibility of remedies. Resistance to change comes from concerns that it will be disruptive or unaffordable to fix the problem. That is not true in this case, said Dr. Holdren, but education is needed to overcome that resistance.

Dr. Holdren added that the difficulty of interdisciplinary work poses another big challenge. It is essential that insights from a wide variety of disciplines be brought to bear around antibiotic-resistant bacteria, and it may be necessary to draw in more expertise on social and behavioral sciences. Communication across boundaries is always difficult, but the Advisory Council members are all experienced with interdisciplinary communication.

Dr. King said achieving the goals requires not only interdisciplinary work but also public-private partnerships that engage, for example, academia and other communities. He asked how such collaboration should be developed. Dr. Holdren responded that President Obama has stressed partnerships across sectors, disciplines, and nations since he took office. In an early cabinet meeting, President Obama explained his view that for some initiatives, the challenges are so great and the resources so limited that partnerships are the only option. Dr. Holdren said that President Obama is a strong supporter of partnerships across sectors, and such efforts have met with considerable success (with an “all hands on deck” approach). The convening power of the White House is extraordinary, said Dr. Holdren.

### **Remarks from the United States Department of Agriculture (USDA)**

#### **Catherine Woteki, Under Secretary of Agriculture, Research, Education and Economics, USDA**

Dr. Woteki said antimicrobial resistance is one of the most challenging and vexing issues at the interface of animal and human health. She thanked the Council on behalf of USDA Secretary Tom Vilsack, who wished to assure the group that USDA will listen and pay attention to its advice. Dr. Woteki said USDA plays dual roles, protecting agricultural and especially animal health as well as public health. The department relies on science- and data-based approaches to guide decision-making. It has embraced the One Health approach and is particularly pleased that the National Action Plan also embraces the One Health approach for combating antibiotic-resistant bacteria. We are organized within the department and the One Health working group helped develop the National Action Plan and the implementation plans and will support the work of the Advisory Council.

Dr. Woteki said that in 2012, she requested USDA begin a review of research and a monitoring program on antimicrobial resistance. In talking with stakeholders, it became clear that USDA was making some decisions without sufficient data. Since then, USDA has been working to fill gaps in knowledge and data. The resulting report of the stakeholder meeting has been the basis of USDA's work under the National Action Plan and the framework for all USDA actions. The agricultural parts of the National Action Plan focus on research and development (R&D), education and outreach, and surveillance. Through R&D, efforts are being made to identify alternatives to antibiotic use, such as vaccine development, and effective management practices for animal agriculture. Also, USDA is seeking to better convey findings to inform decisions by farmers and ranchers on managing herd health. Active surveillance and monitoring of antibiotic resistance are needed to measure progress.

Dedicated long-term funding is the main challenge to conducting the work outlined in the National Action Plan, said Dr. Woteki. While USDA has in-depth knowledge about antibiotic resistance, some of the issues are complex. There is much to learn about how bacteria develop resistance and the impact on human, animal, and environmental health that will guide efforts to mitigate resistance.

## **Remarks from the Department of Defense (DoD)**

### **Jonathan Woodson, Assistant Secretary of Defense for Health Affairs, DoD**

Dr. Woodson expressed thanks to the Council members from DoD Secretary Ashton Carter. He noted that the progress to date on the National Action Plan required tremendous coordination within and across government agencies. He suggested thinking about the expertise not currently represented on the Council, for example, in social science and bioinformatics, needed to address issues such as changing behavior at the point of the patient encounter, where important discussions about the use of antibiotics occur. The progress described by Dr. Holdren is a testament to those involved and to the effectiveness of interdisciplinary collaboration, said Dr. Woodson.

Dr. Woodson said a recent meeting in Seoul, Korea, resulted in agreement by 45 countries to address the GHSA, including combating antibiotic resistance. Representatives from the National Security Council, HHS, CDC, the State Department and others leaders, demonstrated how seriously the entire USG takes this issue and the importance of addressing it internationally. A later meeting in Vietnam on the interactions between military and health issues underscored the importance of recognizing that diseases do not respect organizational boundaries or national borders.

Fighting infectious disease is embedded in the roots of DoD, said Dr. Woodson, but the department cannot do it alone. He described three relevant activities. First, DoD plays an important role in strengthening global surveillance capabilities. Its Multidrug-Resistant Organism Repository and Surveillance Network (MRSN) has 30,000 characterized isolates and 1,500 genomes in its database. This data collection has been critical in helping those in need of health care. It is clear that changes that come about during wartime provide a foundation for improving health care for the American public at large, said Dr. Woodson. He noted that DoD is establishing a policy to use the MRSN to facilitate reporting on antimicrobial resistance and antibiotic use to all military treatment facilities worldwide and contributing to the



database of the National Institutes of Health (NIH) and to upload laboratory data and antimicrobial use data to the National Healthcare Safety Network (NHSN). Second, the Armed Forces Health Surveillance Center's Global Emerging Infections Surveillance and Response System (AFHSC-GEIS) has long monitored global issues that might affect service members and others. It facilitates response to issues of concern for host nations. Through the GEIS, DoD is supporting bacterial surveillance efforts with partner laboratories in and outside the United States. The AFHSC, in which GEIS resides, was brought into the Defense Health Agency in recognition of its important role in DoD's health system and also in supporting interagency efforts.

Finally, DoD supports research on novel diagnostic, screening, and therapeutic options. These include collaborations with FDA and others to develop advanced bioinformatics and sequencing capabilities. Dr. Woodson concluded that DoD seeks to advance activities that support the vital work of the Advisory Council and the federal interagency task force.

## **Remarks from HHS**

### **Wanda K. Jones, Dr.P.H., Principal Deputy Assistant Secretary for Health, HHS**

Ms. Jones appreciated the diversity of experience and expertise of the Council members as well as the representation of numerous entities, because the serious problem of antimicrobial resistance affects everyone. Antimicrobial resistance in critically ill patients increases the risk of death, disability, and length of stay in health care facilities and also increases costs. It must be addressed to reduce costs to providers and to families. One out of five emergency department visits is the result of adverse drug events caused by antibiotics. The poor, the elderly, and those in long-term care facilities are at highest risk for antibiotic-resistant bacteria, and they are among society's most vulnerable populations, said Ms. Jones. It is important to spread this knowledge and to ensure that the work of the Council and others has real-world impact. It is also important that antibiotics remain a strong, useful tool when needed that can reduce suffering.

Ms. Jones hoped the Council would provide guidance to ensure that critical information or key partners are not left out of the discussion. She said that combating antibiotic-resistant bacteria requires smart, principled leadership, such as that provided by Secretary Burwell. Ms. Jones said Secretary Burwell cares passionately about the work that HHS does, and she is willing to hold staff accountable and ask the tough questions. Ms. Jones summarized Secretary Burwell's background by way of introduction.

## **A Healthier Nation: Combating Antibiotic-Resistance**

### **Sylvia Mathews Burwell, Secretary, HHS**

Secretary Burwell thanked the Council members and all the partners in this effort. She noted that the numbers around antibiotic resistance are staggering. Every year, at least two million people become infected with antibiotic-resistant bacteria, and 23,000 die as a direct result. Secretary Burwell shared that this issue is personal for her; her uncle was infected with methicillin-resistant *Staphylococcus aureus* (MRSA) last April, which complicated an existing medical condition and led to his death.

Antibiotics are the foundation on which modern medicine was built. Before antibiotics, a simple cut could take a life. With the ability to fight infections, surgery became safer, and organ and

bone transplants became possible. Now, every incomplete prescription or inappropriate use of antibiotics poses a challenge to health security. Overuse and misuse are further complicated by the use in both humans and food-producing animals.

The risk of antibiotic-resistant bacteria is real, and it is playing out now. In hospitals and cities all over the world, the situation is urgent, and the solution will not be easy, said Secretary Burwell. She noted that the PACCARB can boast of some of the finest minds in medicine and science. The members were selected following a highly competitive selection process. Approximately 300 candidates were reviewed for just 15 member positions, plus the five agency representatives and 10 ex officio members. The Council will provide advice and recommendations to help the National Action Plan and the National Strategy make an impact on the five goals described earlier.

Secretary Burwell said that international partners at recent international meetings about the Global Health Security Initiatives (GHSI) have expressed support for combating antibiotic-resistant bacteria. HHS has already released new guidelines for nursing homes on improving antibiotic prescription practices to reduce inappropriate use and protect residents from the consequences. A new strategic alliance with the private sector is underway to speed development of new drugs to treat antibiotic-resistant infections. The challenge is great, said Secretary Burwell, but so is the will to meet it, she concluded.

## **Interagency Panel Discussions: National Strategy and Action Plans for Combating Antibiotic-Resistant Bacteria Agency Updates**

Dr. Gellin said the National Action Plan set the framework for the PACCARB. The inaugural meeting provides an opportunity to hear from federal partners about progress toward each of the five goals. The formal progress report required by the National Action Plan will be presented to the PACCARB when it is finalized.

### **Goal 1: Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections**

*Beth P. Bell, M.D., M.P.H., Director, National Center for Emerging and Zoonotic Infectious Diseases, CDC*

Dr. Bell explained some of the major gaps related to antibiotic-resistant infections:

- There is limited national, state, and federal capacity to detect, prevent, and respond to urgent and emerging antibiotic resistance threats.
- Data on antibiotic use in human health care and in agriculture are not systematically collected.
- Programs to improve antibiotic prescribing are not widely implemented in the United States.
- There is no systematic international surveillance of antibiotic resistance threats.

CDC's core activities in this area revolve around prevention, stewardship, and surveillance. Public health infrastructure is needed for antibiotic resistance prevention in health care. Federal health entities and state health departments can play a unique, critical role in combating antibiotic resistance through existing state health-care-associated infection (HAI) programs and

their coordinators. Through education and outreach, CDC is raising awareness about the need for better coordination and cooperation between public health authorities and health care providers. One model showed such cooperation could decrease the number of carbapenem-resistant *Enterobacteriaceae* (CRE) cases by 75 percent. The Prevention Epicenters Program at CDC supports innovative research on topics for which knowledge gaps persist, such as the potential for reducing the risk of MRSA with widespread adoption of bathing with antiseptic soap.

Tracking antibiotic use is key to setting national targets and providing feedback to evaluate the success of efforts such as antibiotic stewardship programs in hospitals (developed from guidelines created by CDC). Also, CDC is working on decision support for appropriate prescribing in Department of Veterans Affairs (VA) medical centers. It is seeking to add a measure of antibiotic use to the NHSN and to include antibiotic use and resistance in HAI prevalence surveys. Last year, CDC released guidelines on antibiotic stewardship in hospitals; a comparable guide for long-term care facilities will be published this year.

Consumer and provider engagement through efforts such as the White House Forum and the annual Get Smart about Antibiotics week are central to achieving the goals of the National Action Plan. Dr. Bell said CDC needs the substantial financial support for its prevention, stewardship, and surveillance programs proposed in the President's fiscal year (FY) 2016 budget (\$264 million for CDC programs, \$14 million of the NHSN).

*Peter Lurie, M.D., Associate Commissioner for Public Health Strategy and Analysis, FDA*

Dr. Lurie focused on several FDA activities related to antimicrobial resistance. First, regarding new product development for human drugs, the agency is streamlining regulatory processes for updating and approving antibiotic susceptibility testing (AST) devices to help guide clinician decision-making. It is considering the use of an FDA website, rather than product labeling, to provide information about the threshold for antibacterial resistance.

Second, to minimize antibiotic resistance related to veterinary practice and agriculture, FDA implemented industry guidance eliminating the use of medically important antibiotics for growth promotion in animals and bringing use of medically important antibiotics in animal feed and water under the oversight of veterinarians. To ensure public awareness of these new regulations, FDA now has a website listing affected products with periodic updates. Every animal drug company has committed in writing to making changes, and many drugs have already been withdrawn.

Dr. Lurie said that 30 percent of medically important antibiotics used in animal feed or water have at least one use that includes indefinite duration, which is inconsistent with judicious use. The agency is evaluating whether alternative approaches, such as vaccination, are preferable.

Finally, FDA is engaged in stakeholder outreach and education (e.g., through websites, meetings, webinars, and stakeholder teleconferences) to meet the National Action Plan objectives to ensure animal producers and veterinarians receive information and training to support changes in antibiotic use. It is working to communicate the new VFD through mechanisms that are easy to understand and to improve the standardized VFD form. The agency is collaborating with various stakeholders to disseminate education about new guidance, develop training modules, and reach out to states.

*Gary Roselle, M.D., Program Director, Infectious Diseases, Veterans Health Administration, VA*  
Dr. Roselle explained that the Veterans Health Administration (VHA) has three prevention initiatives overlapping and longstanding programs aligned with Goal 1. Its Multidrug-Resistant Organism Prevention Initiative, which began in 2007, has changed the culture at VA, expanding from its initial focus on MRSA to *Clostridium difficile* and recently to CRE. The initiative led to dramatic drops in MRSA HAIs in and outside of intensive care units (ICUs).

The agency's antimicrobial stewardship initiative, chartered in 2011, requires all facilities to establish prudent prescription practices. The initiative includes monthly education teleconferences, online guidance, and sample policies and procedures. Currently, 49 VA facilities are successfully reporting to the NHSN's antimicrobial use module. Since the stewardship initiative began, VHA has seen big declines in ICU infections, thanks to less antibiotic use.

In the future, VHA plans to develop targeted guidance for its Multidrug-Resistant Organism Prevention Initiative. It will expand its antimicrobial stewardship programs to outpatient and long-term care. Finally, it will increase its capabilities to share VHA data with key stakeholders.

*David Smith, M.D., Deputy Assistant Secretary of Defense for Health Readiness Policy, DoD*  
Dr. Smith emphasized that DoD has a significant stake in addressing the threat of antibiotic-resistant bacteria because of its duty to protect the 9.5 million beneficiaries who use the military health system. Around 2003, when DoD was seeing an influx of casualties from the wars in Iraq and Afghanistan, health care providers had to deal more frequently with antibiotic resistance. Broad-spectrum antibiotic use has been correlated with increased resistance to *Escherichia coli* and *Acinetobacter* species infections in the military health system, driving home the importance of stewardship, said Dr. Smith.

To determine what constitutes appropriate antibiotic use and to support stewardship, DoD created a multidisciplinary working group to formalize policy and implementation around antibiotic use. It is also analyzing data across its system. First, data are gathered through the MRSN, a centralized reference laboratory that collects and characterizes isolates from across the military health system. The MRSN is a vital part of collaboration with other USG partners, academia, and international partners. It was recently expanded to harmonize definitions and criteria with those of CDC and WHO on high-threat bacterial pathogens. The MRSN is collaborating with VA to share data on patients navigating both systems. A pilot project is underway to allow MRSN to report data directly the NHSN.

Second, the AFHSC-GEIS is the public health arm for the whole DoD. It provides a platform for communication with international partners. Its surveillance and monitoring support MRSN and other partner commitments to stewardship. Dr. Smith concluded that DoD has a robust system for evaluation that feeds its work and future research.

*Melissa Miller, B.S.N., M.D., M.S., Medical Officer, Division of Healthcare-Associated Infections, Center for Quality Improvement and Patient Safety, Agency for Healthcare Research and Quality (AHRQ), HHS*

Dr. Miller said that as part of its mission to improve patient health through quality health care, AHRQ supports research on reducing transmission of drug-resistant infections, implementing effective stewardship, and reducing HAIs. It also supports translation of research findings into tools for providers. In 2015, AHRQ more than doubled funding of research on antibiotic-resistant bacteria over 2014, consistent with the objectives of the National Action Plan.

To prevent transmission, AHRQ has new and ongoing projects to reduce transmission of MRSA in households and *C. difficile* and CRE in hospitals. In the area of effective stewardship, AHRQ projects are addressing antimicrobial use in dialysis units, stewardship interventions in nursing homes, and personalization of antibiotic stewardship to individual patients. To prevent resistant infections, AHRQ projects are focused on decolonization studies in multiple settings, prevention of MRSA in long-term care, and improved use of antibiotics for urinary tract infections in nursing homes. Results from completed studies have been translated into a guide for antibiotic stewardship in nursing homes that will become widely available in 2016. Toolkits for preventing *C. difficile* and CRE infections are already available.

Prevention initiatives from AHRQ combine research on HAIs with promotion of proven methods for preventing infections. Its Comprehensive Unit-Based Safety Programs (CUSP) addresses various areas of patient safety. One effort to reduce central-line-associated bloodstream infections demonstrated more hospital units can reduce infections down to zero. Each of the initiatives under this program will likely develop resources that can be disseminated and translated into provider toolkits.

To further the research agenda around antibiotic-resistant bacteria, AHRQ plans to gather experts and stakeholders to identify knowledge gaps for prevention of antibiotic-resistant HAIs and suggest potential interventions. Dr. Miller anticipated a meeting would take place in spring 2016.

#### *Council Member Q&A*

Dr. Blaser said Sweden has a much lower use of antibiotics than the USA, and he suggested looking more closely at the effects of variation in prescribing practices in this country. He believes that getting a handle on such variation could decrease the selective pressure that creates resistance. Dr. Miller responded that improving prescribing requires better information within a state about unequal geographic distribution, indications, and uses. She noted that CMS and others have a long history of using information to drive practice, but to do so require a focus on one identified driver. Dr. Miller said AHRQ has proposed improving patient data so that interventions can be more precise. Currently, there is a good model in HAI measurement and tracking.

Dr. Miller added that AHRQ has developed a program, Targeted Areas of Prevention (TAP), which enables assessment of variations in practice at the facility level. Along with CMS' Quality Innovation Networks and states, AHRQ is working closely with individual facilities to understand the reasons for variations in antibiotic use. Dr. Miller said there is an NHSN module on antibiotic overuse and a National Quality Forum (NQF) measure, which will help track data. Dr. Miller concluded that improving data collection and reporting is a foundation for progress.

Dr. Roselle pointed out that it is easier to track antibiotic use in hospitals than in outpatient settings. As a single provider, VA has more access to information in various settings. Dr. Blaser noted that most antibiotic use is prescribed by private providers.

Alicia R. Cole said California has begun gathering and using data to identify and help low-ranked hospitals. She asked whether CDC is tying its guidelines or requirements to grant funding. Ms. Cole noted that public health departments cannot work with hospitals that have high infection rates and high antibiotic use rates unless the hospitals invite them to collaborate. She asked whether CDC would consider requiring that grant recipients follow guidance to reduce infections. Dr. Bell agreed with the importance of tying grant funding to performance. Overall, she said, CDC has set aggressive targets to reduce infections.

Thomas R. Shryock, Ph.D., asked for data on patient clinical outcomes that would shed light on resistance or susceptibility. Dr. Bell said CDC surveillance data collect clinical outcomes, primarily hospitalization and mortality. There are some data on organisms—for example, infection with certain strains more frequently results in hospitalization. Some of CDC's data are available online, said Dr. Bell.

Ramanan Laxminarayan, Ph.D., M.P.H., asked whether FDA will monitor the phase-out of use of antibiotics for animal growth promotion or just change its labeling. Dr. Lurie replied that FDA plans to monitor current antibiotics sold for commercial use and is trying to expand its understanding of scenarios of antibiotic use on farms. It is also taking part in the National Antimicrobial Resistance Monitoring System (NARMS) to detect antibiotic resistance in different settings.

John H. Rex, M.D., noted that variations in prescribing practices are strongly influenced by cultural and social anthropological issues, and fostering change requires different communication strategies in different societies. He asked whether research has taken into account social and cultural factors affecting antibiotic use and how to change behavior. Dr. Miller said several AHRQ-funded studies on stewardship have looked at whether physicians are given appropriate information and take antibiotic resistance information into account. The agency is also conceptualizing around culture change mechanisms.

Dr. Smith said DoD works to educate providers and patients but could be “smarter” on cultural and social issues. He noted that efforts to fight the Ebola virus finally gained traction when interventions were designed that took into account local burial practices.

Robert A. Weinstein, M.D., said a recent publication showed a strong association between training and practice. He asked what efforts are underway to educate medical students and residents about appropriate antibiotic use. Dr. Bell said CDC is working with some professional societies to improve how the topic is addressed in medical schools. She said CDC wants to intervene early in a clinician's career, so medical school is the logical place. Dr. Lurie added that there is active outreach to veterinary medical schools as well.

## **Goal 2: Strengthen National One-Health Surveillance Efforts to Combat Resistance**

*David Goldman, M.D., Chief Medical Officer and Assistant Administrator, Office of Public Health Science, Food Safety and Inspection Service (FSIS), USDA*

Dr. Goldman said USDA's Agricultural Research Service (ARS), Animal and Plant Health Inspection Service (APHIS), and FSIS will lead the department's efforts around the National Action Plan. Success will depend on existing and new collaborations between USDA and FDA, whose work in this area is interdependent.

To achieve National Action Plan objective 2.3 around standardized AST and characterization of pathogens, APHIS has surveyed veterinary diagnostic laboratories to assess current practices and capacity. It is working with stakeholders on recommendations for standardizing testing and collecting and sharing data. All the agencies are looking at alternative methods, such as whole genome sequencing, to screen for antimicrobial resistance. To meet the 1-year milestone for objective 2.3, USDA and FDA are assessing current capacity and protocols of the National Animal Health Laboratory Network (NAHLN) and Veterinary Laboratory Investigation and Response Network (Vet-LIRN), respectively. Meeting the 3-year milestone to support laboratory capacity development and training in AST requires additional funding.

National Action Plan objective 2.4 calls for increased monitoring across the food production chain, which aligns with the goals of ARS' NARMS. The National Action Plan provides an opportunity for ARS, APHIS, and FSIS to improve data analysis, although more resources are needed to support collaborative efforts. Currently, USDA is seeking input on a proposal for expanded monitoring, and FSIS is increasing meat sampling efforts. The 3-year milestone for objective 2.4 calls for even more data collection from food producers and processors, and Dr. Goldman again noted that meeting the goal depends on the budget.

Dr. Goldman said the biggest challenge USDA faces is the lack of long-term funding. He proposed several questions for consideration that would require additional support for investigation:

- What is the appropriate role of molecular versus culture-based surveillance and characterization for antimicrobial resistance?
- What is the appropriate investment mix for the government across the areas of agriculture versus human health and among research versus surveillance versus outreach/education?
- What are some solutions around obstacles (i.e., limited resources) to collecting antimicrobial use data and samples for characterizing antimicrobial resistance?
- With limited resources, what would be a good model for a public-private partnership for collection of antimicrobial use and resistance data? What other options are available?

*William Flynn, D.V.M., M.S., Deputy Director for Science Policy, Center for Veterinary Medicine, FDA*

At FDA, the Center for Veterinary Medicine is responsible for regulating animal drugs, devices, and food additives; it works closely with CDC and USDA on NARMS and Vet-LIRN.

Regarding National Action Plan objective 2.3, FDA is working with USDA to assess the capacity of Vet-LIRN and APHIS' NAHLN. Expanding capacity depends on funding, said Dr.

Flynn. For National Action Plan objective 2.4, FDA is taking a multipronged approach, enhancing existing data and collaborating with USDA and CDC to collect farm data.

Existing data sources have some limitations and gaps. For example, antibiotic sales and distribution data do not provide sufficiently granular information about why antibiotics are used and under what conditions. The NARMS has robust trend information on resistance patterns, but it reflects animal data only and is not connected to data about antibiotic use from the samples collected. Dr. Flynn said FDA, USDA, and CDC have established a working group to explore how to fill data gaps to get a better picture of antibiotic use in farm settings.

In addition, FDA has increased the level of detail it provides in its annual reporting about antibiotic sales and distribution data. The agency recently proposed a rule that would require estimates of sales data according to animal species. Dr. Flynn said getting more data from the farm level is key. As noted earlier, FDA plans to double its testing of retail meat through the NARMS. It has already improved NARMS reporting and is moving toward an integrated report for public presentation. (Currently, data are available from FDA for research and other purposes.) Dr. Flynn concluded that improved data collection, specifically sales and distribution data, will enhance understanding of the context of antibiotic use and assist in assessing progress toward goals, but the availability of resources is a critical limitation.

*Beth P. Bell, M.D., M.P.H., Director, National Center for Emerging and Zoonotic Infectious Diseases, CDC*

Dr. Bell described the three main complementary surveillance systems CDC relies on for antimicrobial resistance monitoring. First, the NHSN gathers data from health care facilities on infections and drug resistance in health care settings. It has been pivotal for hospital improvement efforts. Second, NARMS tracks changes in the susceptibility of bacteria to antibiotics through testing of humans, food animals, and meat. It allows tracking of antibiotic resistance patterns by demographic characteristics. Third, the Emerging Infections Program (EIP) is a collaboration across 10 state health departments that provides access to isolates for testing and detailed clinical data. It serves as an early warning system for new and emerging threats and facilitates research.

In addition, CDC's Clinical and Environmental Microbiology Laboratory serves as a national and international reference laboratory for AST, diagnosis of pathogens causing HAIs and antibiotic-resistant infections, development and evaluation of detection methods for emerging resistance, and assessment of contamination of the health care environment. Recently, CDC proposed a regional laboratory network to more rapidly detect outbreaks caused by antimicrobial-resistant pathogens, but the network depends on funding. Together, CDC and FDA launched an antimicrobial-resistant isolates bank. It has 160 isolates so far and has been a popular resource for researchers and manufacturers.

*Paige Waterman, M.D., FACP, FIDSA, Antimicrobial Resistance Lead, AFHSC-GEIS, DoD*

Dr. Waterman said DoD believes that high-quality centralized laboratory analyses save money and time and provide reliable data for surveillance efforts. Enhancing existing processes will improve quality of care and overall patient safety efforts, including judicious use of antibiotics. Dr. Waterman said DoD's MRSN is a unique asset that offers a vast repository of resistant isolates (more than 30,000). It has an advanced bioinformatics pipeline and can be used for



genetic characterization. Since MRSN was established in 2009, CRE rates in military health facilities have decreased, in part because of aggressive surveillance and information dissemination to DoD health care settings, resulting in modification of infection control and prevention policies. Plans are underway to expand access to the MRSN's translational database. The MRSN contributes to national databases and facilitates DoD collaboration with other partners.

Dr. Waterman noted that the Navy-Marine Corps Epi Data Center, Army Pharmacovigilance Center, and MRSN together provide data on antibiotic use and susceptibility that are reported to the NHSN. They also inform DoD's stewardship policies and procedures.

Finally, the AFHSC-GEIS, DoD's public health surveillance arm, guides efforts on the One Health approach. Most of the efforts currently are focused on Southeast Asia, but DoD anticipates expansion. The systems includes food safety-certified veterinarians (military working dog population), demonstrating the effort to close the data gap between human and animal health.

#### *Council Member Q&A*

Dr. King asked whether any of the efforts address the use of antibiotics in dogs and cats. Dr. Flynn said the One Health approach takes companion animals into account. Currently, efforts are focused on the foodborne pathway to antibiotic exposure, but Dr. Flynn said additional emphasis is needed on the role of companion animals.

Kent E. Kester, M.D., FACP, FIDSA, FASTMH, noted that CDC proposes to develop a network of regional laboratories and recently established an isolate bank, yet DoD has thousands of isolates in its MRSN. Given constrained budgets, Dr. Kester asked where the panelists see logical leverage points or potential for collaboration. Dr. Bell responded that CDC aims to take advantage of state public health infrastructures, not brand new labs, to bring together groups and data collections. She said there is a need for an integrated, organized approach to population-based data to facilitate comprehensive understanding. Currently, there is good information and a clear understanding of the situation for some areas of the country but not for others. Sometimes, the gaps become clear because of disease outbreaks, said Dr. Bell. She acknowledged that resources are limited, and the National Action Plan aims to spur collaboration across government agencies. The *Listeria* initiative is an example of multiple agencies working together in real time.

Dr. Blaser asked whether the NARMS allows researchers to look into questions about antibiotic residue in meats that could lead to resistance in recipients. Dr. Goldman responded that USDA manages the National Residue Program, a longstanding collaboration across agencies to look for evidence of residue of veterinarian drugs in meat products. The program seeks to identify drugs that are not permitted for use or that seem to be reaching tolerance levels, but it also gathers data on residues that are under tolerance levels. A proposed pilot project would look at the existence of residue and resistance in the same samples to test the hypothesis Dr. Blaser described.

Randall Singer, D.V.M., M.P.V.M., Ph.D., asked how long new data streams would have to be in place before one could see links between trends and antimicrobial resistance. Also, given the number of so-called bug-drug combinations, he wondered how long it would take to see the impact of changes on resistance. Dr. Flynn said FDA is seeking such input from stakeholders

now. He hopes to manage expectations around data and emphasize the need to gather sufficient data before drawing conclusions. In the short-term, data are needed to determine whether proposed strategies are being implemented and, if so, whether they can be verified. The more complicated piece is determining whether strategies are having the desired effect (changing antibiotic use and mitigating resistance). As the complexity increases, more time is needed to gather data, evaluate them, identify trends, and evaluate the impact of interventions. Dr. Bell agreed that the process is complex, but she said some good examples exist in the animal sphere. For example, withdrawal of cephalosporins had a relatively quick impact. Dr. Flynn agreed that there are instances that demonstrate rapid responses, but it is challenging when data are collected across such a large and varied industry.

Elizabeth Allen Wagstrom, D.V.M., M.S., said the pork industry is very interested in the efforts to improve data. Some challenges are practical, such as the difficulty of following a group of animals through the slaughter process and identifying antibiotics in the end-product. It is difficult to analyze how antibiotics are used and to link that use to the end-product, she noted. Dr. Wagstrom asked what approach will be taken to inform decision-makers as USDA ramps up from the pilot project currently looking at 48 farms to a robust surveillance effort that will provide a significant look at the industry. Dr. Flynn clarified that efforts are underway to ramp up programs to ensure sufficient national representation for drawing conclusions. Along those lines, FDA will look at USDA programs, such as APHIS' National Animal Health Monitoring System (NAHMS), as a model for surveillance and data gathering that is designed to generate reliable information. Resources will be required to design and sustain such a program over time.

Sara E. Cosgrove, M.D., M.S., praised the CDC's antibiotic stewardship module and asked what critical steps are needed to convince the rest of the country's hospitals to use it. Dr. Bell said many hospitals find it difficult to commit to the program because their electronic medical records (EMR) systems are not configured to gather the data needed to support the program. Therefore, CDC is working with major EMR vendors to make it easier for hospitals to capture data electronically.

Dr. Laxminarayan pointed out that antibiotics are a societal resource that the health care system wants to use for maximum societal benefit. He asked whether there is any known benefit of antibiotic use for animal health or economic production. Dr. Laxminarayan believed that the benefits of animal antibiotic use have decreased since farming techniques and animal health have improved, and European models support that belief. Dr. Flynn said there is a need to explore alternative approaches to animal health, such as alternative management strategies to minimize antibiotic use or new animal health products. Dr. Laxminarayan clarified that he questions how much antibiotic use contributes to animal health currently, and Dr. Flynn responded that antibiotics are clearly important for managing animal health conditions. Dr. Flynn added that steps can be taken to reduce reliance on antibiotics, and FDA hopes to further efforts in that direction. Dr. Goldman noted that at least one study by the USDA's Economic Research Service found that antibiotics increase yields and production.

### **Goal 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria**

*Dennis M. Dixon, Ph.D., Chief, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH*

Dr. Dixon said NIAID leads most of the NIH response to the National Action Plan, and much of its work is described in the report [NIAID's Antibacterial Resistance Program: Current Status and Future Directions](#). Among the ideas outlined is the creation of diagnostics to guide the use of narrow-spectrum therapeutics, along with clinical trials to validate new therapeutics. Since 2010, NIAID has supported 12 targeted funding opportunities around diagnostics, including research on HAIs, point-of-care technologies, and drug-resistant bacteria. It has also convened or participated in national and international workshops on diagnostics for antimicrobial resistance. Two currently available diagnostic devices have their roots in NIH research efforts.

Further, NIH's Antibacterial Resistance Leadership Group has led several activities around diagnostics, including support for a breakthrough gene expression signatures study to distinguish viral from bacterial infections and creation of a virtual biorepository that would allow researchers to get clinical specimens on demand. The Antibacterial Resistance Leadership Group is working with FDA and industry on a master protocol to facilitate simultaneous validation of diagnostics across multiple companies. It is also supporting research on the use of procalcitonin as a marker for infection that can identify those who do not need antimicrobials.

Since the National Action Plan went into effect, NIH has funded nine grants supporting partnerships to develop diagnostics to address antimicrobial resistance. The challenges to achieving the goals of the National Action Plan include the limits of detection and the difficulty of making clinical decisions about colonization versus infection (e.g., in the case of pneumonia). In addition, clinical uptake remains a challenge, as does reimbursement uncertainty.

The NIH Office of the Director and HHS' Biomedical Advanced Research and Development Authority (BARDA) are developing the antimicrobial resistance Diagnostic Challenge Competition, which offers a \$20 million prize, to stimulate new research in the field. Public input on the terms of the competition and the parameters of an ideal diagnostic test are welcome.

*Steven Gitterman, M.D., Ph.D., Medical Officer, Center for Devices and Radiological Health, FDA*

Dr. Gitterman described a "golden age" of development of antimicrobial resistance diagnostics, with many molecular/multiplex devices available that address the National Action Plan objectives. Most of them analyze direct specimens and allow integrated sample preparation. Batch and random access devices are available, so they can be used by small laboratories or those with high throughput, and many of the devices rapidly detect common markers of resistance. However, the costs of these devices are high, which affects their adoption, and clinical interpretation of the results remains challenging.

For regulatory progress, Dr. Gitterman said FDA provides guidance on diagnostic devices and revises recommendations in response to experience and pre-submission queries. When appropriate, FDA reclassifies products to reduce unnecessary burdens or spur better product performance. Recently, CLIA requirements on molecular diagnostics were waived, allowing

their use in doctors' offices. Newer devices that allow direct detection from blood have increased sensitivity and have high negative predictive value (which is especially important for clinical trial enrollment and efficiency). Cost, accessibility, and the blood volume required limit uptake of these devices.

As new products emerge, biomarker repositories will be invaluable for manufacturers seeking to update their devices. The Consortium for Tuberculosis Biomarkers and the FDA-CDC antimicrobial resistance isolate bank will play an important role in diagnostics development. The next-generation sequencing database may also be a valuable tool.

Among its current activities, FDA has provided guidance on coordinated development of AST devices. It has co-hosted workshops on interoperability with CDC and NIH and is planning a workshop on non-microbial biomarkers for infection. Dr. Gitterman concluded that FDA collaborates with numerous federal partners and has a very active pre-submission process with NIH and industry players.

*Shari Ling, M.D., Deputy Chief Medical Officer, CMS*

Dr. Ling pointed out that from CMS's perspective, increasing the availability of diagnostics requires coding, coverage, and payment policies. To spur regulatory efficiency, CMS and FDA are pilot-testing a parallel review process for rapid review of promising technologies. Under this process, FDA announced approval of Cologuard, a stool-based colorectal screening test, on the same day that CMS announced a national coverage determination on Medicare payment for the test.

Dr. Ling explained that Medicare determines inpatient and outpatient service payments prospectively, not on a cost basis, so it is a challenge for CMS to provide incentives for new technology. Still, some payment vehicles are available. First, the New Technology Add-On Payment can be applied to new technology that demonstrates improvements in diagnosis and management for Medicare beneficiaries (largely hospital populations). This approach may lead to a higher payment rate for 2–3 years. Second, a similar vehicle is available for outpatient settings through new technology Ambulatory Payment Classifications and pass-through payment status. This year the agency published the [Innovators Guide to Navigating Medicare](#), which provides guidance on obtaining codes, coverage, and payment.

*Council Member Q&A*

Given that in the case of antibiotic-resistant bacteria in outpatient settings, a major goal of patient care is ruling out conditions that do not require a drug, Dr. Rex asked how a clinician can demonstrate to CMS that he improved diagnosis or treatment. Dr. Ling acknowledged the challenge of the construct, noting that it extends beyond payment to the function of CMS systems. Diagnosis may occur in the outpatient setting, while the resulting improvement occurs in a different setting or practice. Dr. Ling said CMS and others need to think about how to measure and assess efforts to avoid overuse of antibiotics, especially when data may not come from the same settings.

Dr. Blaser said medical care in the United States involves a series of disconnects. For example, in pediatric practice, an inexpensive antibiotic may seem preferable to a \$200 diagnostic test, even though the latter could help cut unnecessary usage and cumulatively save millions of

dollars in downstream medical costs. He asked how to change the price model. Dr. Ling responded that it is a new construct that each provider contributes to patient care in the health system. The question is not only how to improve outcomes for patients currently in the clinic but also for the rest of those in the practice, the community, and the health care system. Dr. Ling said conversations are changing because the incentives are changing. Alternative payment models speak to ways to improve outcomes in a population. The challenge is in the data. Understanding antibiotic use and prescribing practices is critical for incentivizing behavior. The issue goes beyond payment to the technical components needed to change behavior. Change will come from those who can lead from the inside to help systems work toward meaningful improvement. Dr. Dixon added that one study by the Antibacterial Resistance Leadership Group gave credit to clinicians for using fewer antibiotics (e.g., a shorter course or less exposure). It is possible to create mechanisms that track and value the benefit of diagnostics, he said.

Dr. Laxminarayan noted that PCAST recommended appointing a White House director of national antibiotic policy. While there seems to be some good collaboration and individual agencies have done some great work, Dr. Laxminarayan said it is not clear how agencies coordinate with each other—for example, how work on diagnostics connects with CDC stewardship efforts. He asked whether a White House director would be helpful. Dr. Dixon said he thinks the key value of the PACCARB is its ability to play that coordinating role by looking at the integration of the components.

Dr. King noted that innovation is not just about technology but also refers to innovations that add value. Given the new platforms aiming to improve surveillance and standardization, lower costs, and increase integration across laboratories, a major innovation could be the application of new platforms to animals, humans, and the environment. Dr. Dixon said the interagency task force can help by encouraging uptake of new platforms across agencies. Dr. Ling agreed that the PACCARB can help synthesize some efforts underway. She noted that CMS just proposed antibiotic stewardship as part of its rules for long-term care facilities covered by Medicare, and a hospital version is in the clearance stage. Diagnostic tests can be used in any setting in a complementary way, said Dr. Ling.

Dr. Blaser noted that it is up to clinicians to interpret the results of diagnostic tests and distinguish between colonization and disease. However, it may be that better training is needed for all clinicians—including dentists, nurses, and veterinarians—on how to make such distinctions. He asked which agency would take the lead on this issue, and Dr. Gitterman said an upcoming meeting seeks to address it. Going back to the economic analysis question, the field of decision science—mapping out the ramifications of various options and costs—is a rapidly moving area. It involves tools and models to support decision-making, Dr. Gitterman noted.

#### **Goal 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines**

*Dennis M. Dixon, Ph.D., Chief, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Diseases, NIAID, NIH*

Dr. Dixon again referred to the report [NIAID's Antibacterial Resistance Program: Current Status and Future Directions](#), which describes intensified efforts to translate research into practice and highlights several new ideas for scientific exploration relevant to antibiotic-resistant bacteria. Since 2010, antibacterial development has been a top priority for NIAID, which has funded 18

projects on therapeutics (targeted funding opportunities). It has also held two workshops each on development of a vaccine for *Staphylococcus* infection and managing bottlenecks in drug development.

Dr. Dixon said NIAID has invested in extensive infrastructure to encourage industry to pursue therapeutics in this area. Over the past 10 years, NIAID has supported product development projects and provided targeted services. For example, NIAID established 9 clinical trial units across the country to support phase 1 and 2 clinical trials of new vaccines and therapeutics. For eligible entities, NIAID will conduct and pay for the trials. Also, the Antibacterial Resistance Leadership Group develops a research agenda around topics selected by NIAID, then prioritizes and designs trials on issues of national and worldwide significance. Recent NIH activities include funding for research on systems biology and antibacterial resistance. For example, the makers of a novel tetracycline, developed with NIAID support, are seeking FDA approval. Also, NIH has four contracts for therapeutics in the advanced development stage.

In addition, NIH has called for research on nontraditional and host-targeted therapeutics. It also seeks to support new research into bacteriophage therapy and the role of microbiota in infectious disease. Furthermore, NIH is providing preclinical support services for *Staphylococcus* and *Shigella* vaccine candidates and for a defined product for fecal microbiota transplant clinical trials.

In accordance with the National Action Plan objective to leverage existing partnerships, NIH seeks to create a directory of potential partners who can help with study enrollment. It is also working with partners such as FDA and the Antibacterial Resistance Leadership Group to reduce barriers to therapeutic and vaccine development by implementing new processes. Dr. Dixon concluded that the greatest science in the world will not yield a product until a company recognizes the ability to market it.

*Joseph Larsen, Ph.D., Chief, Broad Spectrum Antimicrobials Program, Biomedical Advanced Research Development Authority (BARDA)*

Dr. Larsen described BARDA's role in developing medical countermeasures (vaccines, diagnostics, and therapeutics) for public health emergency preparedness. He said BARDA treats antibiotic-resistant bacteria as a perpetually emerging infectious disease. In 2010, BARDA expanded its focus to antimicrobial resistance; at present, four products developed through public-private partnerships with BARDA are in phase-3 clinical trials. Dr. Larsen emphasized that the partnerships involve a lot of cost-sharing so that the manufacturers have a significant stake in the outcome.

Already, BARDA has made progress in meeting three of the first-year milestones established for it by the National Action Plan. First, BARDA recently expanded its portfolio by partnering with Astra Zeneca in development of antibacterial candidates. Under this partnership, BARDA can adjust its support over time to facilitate joint collaboration and flexible decision-making. BARDA is partnering with the European Union's Innovative Medicine Initiative (which speaks to the National Action Plan's goal on international efforts).

Second response to National Action Plan objectives, BARDA, in collaboration with NIAID, proposed a biopharmaceutical incubator to support a robust pipeline of products to combat

antimicrobial resistance. The incubator would provide entrepreneurial support for small, young companies, but Dr. Larsen said it is unclear whether there is sufficient funding to initiate the program. Third, as part of the Economic Incentives Working Group (established by the National Action Plan), BARDA presented recommendations to PCAST to increase incentives to industry around antibacterial drug development, but Dr. Larsen said it seems unlikely the recommendations will be implemented.

For product development, BARDA requested an additional \$107 million for FY 2016 to expand its current portfolio and partnerships, but again, Dr. Larsen said, the likelihood of funding is uncertain. He concluded that BARDA will continue pursuing public-private partnerships, but additional funding is needed to achieve most of the goals that the National Action Plan established for BARDA.

*Steve Kappes, Ph.D., Deputy Administrator, National Program Staff, Animal Production and Protection, ARS, USDA*

As the agricultural research arm of the USDA, ARS plays a role in understanding the environmental factors that facilitate antibiotic resistance. It takes part in roundtable discussions with USDA, FDA, CDC, NIH, academic partners, industry representatives, and other stakeholders to gather input on strategies to advance collaborative research efforts and develop tools to combat antibiotic resistance. Dr. Kappes pointed out that the agricultural environment must take into account numerous differences across animal species. Achieving National Action Plan milestones requires building on existing partnerships to encourage collaborative research from basic science to clinical testing.

The National Action Plan objective 4.2 to increase research on microbes speaks to the need for better understanding of microbiology in relation to soil and air. Dr. Kappes said USDA is currently funding studies on ecology and animal health. Its National Institute of Food and Agriculture (NIFA) also conducts surveillance, training, and education. Dr. Kappes said USDA recently convened a meeting of experts about the microbiome.

The National Action Plan appoints USDA and others to create an R&D strategy for development of nontraditional therapeutics and vaccines. To this end, ARS and NIFA have planned a workshop. Dr. Kappes described some accomplishments of ARS and NIFA, including a bacteriophage to reduce disease in poultry; a cytokine to control respiratory and parasitic disease; vaccines against mastitis, *Salmonella*, *Campylobacter*, *E. coli*, and coccidia in various animals; and alternatives to antibiotic use for animal health and growth promotion. In addition, NIFA is soliciting proposals for research and outreach programs to target novel alternatives to antibiotics through its flagship Agriculture and Food Research Initiative.

Dr. Kappes asked the Council to consider the following:

- It would be useful to develop a common set of definitions for terms and phrases such as “multidrug-resistant,” “stewardship,” and metrics for successfully reducing antimicrobial resistance to facilitate discussions.
- Given limited resources, what are the most urgent questions or possible solutions that should be addressed with research in developing alternatives to antibiotics?
- What are the obstacles to education and outreach and what are some possible solutions?

*Edward Cox, M.D., Director, Office of Antimicrobial Products, Center for Drug Evaluation and Research, FDA*

Dr. Cox expressed that the antibiotic drug pipeline is fragile, because the area of drug development is scientifically and economically challenging. Under the Generating Antibiotic Incentives Now (GAIN) Act, FDA can designate some products as qualified infectious disease products (QIDP), securing priority review and 5 years of additional exclusivity for the manufacturer if the product goes to market. So far, 87 products have received QIDP designation, 60 of which are unique products, and six (including one antifungal) have been approved by FDA. Dr. Cox cautioned that most drugs that reach phase-1 clinical trials ultimately are not shown to be safe and effective.

Since 2012, FDA has published/revised 11 guidance documents describing recommended pathways for development on multiple topics. One such document focuses on streamlined drug development pathways for unmet need—that is, drugs for patients with few or no alternatives. This guidance reflects some of the ideas proposed by the Infectious Diseases Society of America (IDSA) in its recommendation to create a mechanism of approval for antibacterial drugs targeting a limited population.

To advance the science of clinical trials, FDA is working with the Foundation of the NIH on developing and evaluating endpoints for several infectious diseases, with the Clinical Trials Transformation Initiative at Duke University on trial efficiency and design, and with the Brookings Council on Antibiotic Drug Development to address overarching issues. Dr. Cox said that curating the science supporting clinical trial design and endpoints a key for U.S. research and for harmonizing available approaches internationally.

Among the challenges is the difficulty of developing drugs that target rare species, because it is hard to demonstrate efficacy using normal criteria. However, narrower-spectrum antibiotics could play an important role in fighting antibiotic resistance. Clinical trial networks could provide infrastructure, expertise, and common protocols that could move drug development forward. Such a network could be designed to study basic infections to provide a foundation for future drug development. The current system for updating information about breakpoints is cumbersome. FDA could leverage the work of standards authorities and identify ways to communicate label updates digitally, guiding clinicians in selection of antibiotics and identification of patients for whom additional infection control practices are needed to prevent the spread of resistant organisms.

#### *Council Member Q&A*

Beyond financial hurdles, Helen W. Boucher, M.D., FIDSA, FACP, asked what challenges BARDA faces in establishing an incubator that works in a competitive way. Dr. Larsen said BARDA learned that if it funded another entity to manage its investment, BARDA could not be as involved on a day-to-day basis as it is now with partners. It also learned that funding must be based on milestones and that the funder must be “ruthless” in withdrawing support definitively if needed. Also, half of start-ups fail because of bad management, so business support is just as important as technology support, said Dr. Larsen.



Ms. Cole asked what FDA is doing to ensure patient safety, specifically, how regulators follow up with patients to track unexpected side effects. Dr. Cox said that FDA tries to communicate what it knows and does not know about products when they reach the marketplace. With experimental drugs, FDA knows less. For approved products, FDA maintains a safety database that informs labels and warnings. Once a product is approved, said Dr. Cox, FDA gathers information on its use in the broader population, which is often more heterogeneous than the population involved in a clinical trial. It has a system for reporting adverse events, which helps FDA identify patterns and informs updated labeling. In addition, the FDA sentinel system in development will explore patient experiences with approved drugs. Depending on the drug and nature of adverse effects, FDA may establish patient registries.

Ms. Cole suggested FDA collect unusual events and side effects that health care providers may not deem important enough to report to FDA or drug companies. Such effects can affect a patient's daily life, she noted. Dr. Cox agreed that sometimes people discount adverse effects because they are unexpected.

Michael D. Apley, D.V.M., Ph.D., DACVCP, asked if there are plans to support research on optimal pharmacokinetics/pharmacodynamics (PKPD) to suppress resistance, duration-of-therapy, or body-weight dosing to stretch the utility of current drugs. Dr. Dixon said NIH has targeted PKPD. Some studies have looked at optimizing drug delivery. The scientific community appears to appreciate NIAID's attention to revisiting the use of old drugs, such as colistin, to reduce antibiotic resistance. Dr. Cox added that PKPD is a core part of what FDA reviews and an important tool in the drug development process.

Dr. Blaser suggested USDA partner with the National Science Foundation, the Environmental Protection Agency, and the Department of Energy to study the ecology of farm animals. Dr. Kappes agreed with the need to partner and said it is necessary to look at the microbiome in the agricultural setting. Dr. Blaser suggested that research on narrow-spectrum therapies could target common human infections first (instead of uncommon infections), such as group A streptococcus, pneumococcus, and *S. aureus*. Dr. Cox agreed that studies can go forward in that important area of investigation.

Dr. Rex requested a copy of the Economic Incentives Working Group report to OSTP.

Dr. Wagstrom asked whether there are regulatory pathways in place for alternative antibiotics that treat or prevent disease and promote growth in animals. Dr. Kappes said USDA's highest priority is prevention of disease. Because medically important antibiotics can no longer be for used animal growth production, there is a need for drugs to promote growth in young animals. He said there can be an added health benefit to having drugs for treatment, but a relatively small portion of USDA's budget addresses that topic. Dr. Kappes added that USDA needs more funding for research to identify the mechanisms of disease.

Elizabeth Jungman, J.D., M.P.H., said there was a rumor that FDA would approve limited-population antibacterial drugs without clinical trials. Dr. Cox said clinical trials are part of the approval process. Under current proposals, the standard for determining efficacy is the same, but there is more attention to balancing risk in the face of unmet need (i.e., for people who have no other options).

Dr. Singer said USDA seems committed to the One Health approach, but he would like to see other agencies' portfolios reflect attention to the interaction of animal and environmental issues with human health outcomes. Dr. Dixon responded that NIAID must work within its mission statement but does conduct bridge studies and look at areas of overlap. Dr. Singer pointed out that USDA does not have sufficient budget for the kind of complex study design needed.

Dr. Shryock pointed out that many pharmaceutical companies used to have animal health divisions, so they could leverage their R&D investments across animal and human health. He added that innovative companies have alternative strategies in place to avoid losing money; along those lines, if a drug designed for humans fails clinical testing, it may be appropriate to evaluate its use in animals. Dr. Shryock asked whether BARDA could consider such an exit strategy. Dr. Larsen replied that BARDA is committed to public health preparedness but could take such ideas into consideration. Dr. Dixon added that many human drugs are first tested in animals or rely on animal-based scientific concepts.

Dr. King asked whether any current research is addressing enhancing host response, in either animals or humans. Dr. Dixon said NIH just issued a request for applications for host-based targets for antimicrobial activity. Dr. Kappes said USDA is interested in the topic, but it is relatively expensive research.

#### **Goal 5: Improve International Collaboration and Capacities for Antibiotic-Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development**

*Jimmy Kolker, Assistant Secretary, Office of Global Affairs, HHS*

Mr. Kolker explained that a lot of international entities support the need to manage antibiotic resistance all over the world. The WHO's Global Action Plan directs members to develop national plans to advance local efforts to combat antimicrobial resistance, devise incentives for creation of new therapeutics, and ensure access for those in need of treatment. Numerous international partnerships and summits are addressing antimicrobial resistance.

Through the G7, President Obama called for participant nations to develop antibiotic resistance plans and take part in the GHSA. The GHSA targets include prevention and control of the emergence and spread of antimicrobial resistance through national plans and partnerships. The Transatlantic Task Force on Antimicrobial Resistance (TATFAR) has created a framework for research, mostly among public sector institutions (including FDA, CDC, and NIH), to harmonize criteria for surveillance, analyze patterns, develop innovative approaches, and address key knowledge gaps. It is planning an international meeting this fall.

To enhance international communication about critical events, countries are coordinating data surveillance and analysis to allow for comparisons and to identify gaps. Mr. Kolker said European countries generally apply the precautionary principle, banning a product if it raises concerns, while the United States often takes a risk/evidence based approach. To improve information dissemination, the G7 has committed to review national plans. The Pan American Health Organization will help countries that do not have national actions plans. The GHSA will identify gaps.

Regarding incentives for product development, the United Kingdom has commissioned studies and NIH has forged an agreement with India around antibiotic resistance product development. Mr. Kolker pointed out that even in places where there are a lot of resources and surveillance is a priority, it is hard to get antibiotic resistance on the agenda.. It is challenging to get any organizations interested if efforts are not already underway.

*John Clifford, D.V.M., Chief Veterinary Officer and Deputy Administrator for Veterinary Services, APHIS, USDA*

Dr. Clifford said USDA has contacted international partners to identify their capacity for monitoring and potential training in Latin America. To meet the objective of harmonizing international data submission requirements, USDA is taking part in an international working group on electronic submission of adverse events reporting. This group is discussing global harmonization of pharmacovigilance guidelines and validation procedures for industry reporting of adverse events. USDA is maintaining the U.S. commitment to International Cooperation on Harmonization of Technical Requirements for Veterinary Medicinal Products (VICH) and the Institute for International Cooperation in Animal Biologics (IICAB) and expanding global outreach by participating in annual veterinary biologic training in Iowa. The training includes an overview of the U.S. regulatory process for ensuring the purity, safety, potency, and efficacy of veterinary biologics.

A series of VICH global forums is in the planning stages. Working groups are discussing harmonization of regulatory policies around veterinary biologics and diagnostic test kits. Also, USDA hosted an international meeting jointly with the IICAB on potency specifications.

Dr. Clifford posed the following issues for consideration by the Council:

There are significant challenges to harmonization: data collection is resource-intensive, and data comparisons across regions and countries are often not meaningful.

What does the Council see as the most critical priorities for addressing antimicrobial resistance internationally and what would be some effective mechanisms to address these?

*Lynette Poulton, Director, Office of International Health and Biodefense, Department of State*

Ms. Poulton reminded the participants that antimicrobial resistance is a global concern that fits into the State Department's mission. Its global health diplomacy efforts around antimicrobial resistance include diplomatic, foreign policy, and programmatic engagement to secure greater involvement across all sectors, expand the impact of U.S. global investments, and ensure evidence-based decision-making. The State Department's "whole of society" approach emphasizes the role of civil society, the financial sector, industry, and the faith community. Ultimately, communities and individuals must be engaged in solutions that involve how medicines are prescribed and used.

As Mr. Kolker explained, the USG is involved in numerous multinational efforts. The State Department also facilitates bilateral and regional engagement, using the platform of the GHSA and other mechanisms to call attention to antimicrobial resistance. One key tool has been the use of bilateral science and technology agreements. The USG has established mechanisms with more than 50 countries that support discussion of opportunities for scientific and technical

cooperation. The State Department has been involved in several successful efforts to add antimicrobial resistance research to the agenda.

In those areas where the State Department does fund research or provide technical assistance, it is working to leverage its efforts to complement the work of others, said Ms. Poulton. For example, it has promoted pilot programs in citizen science, such as mapping the lifecycle of antibiotics, which simultaneously increases scientific literacy and provides data. The State Department is working on a faith-based approach with the Vatican to reach areas that the USG cannot. The U.S. Agency for International Development (USAID) has a number of activities aimed at antimicrobial resistance, particularly for tuberculosis, and the State Department works closely with that agency.

*David Smith, M.D., Deputy Assistant Secretary of Defense for Health Readiness Policy, DoD*

Dr. Smith said DoD has research and surveillance networks all over the world to support its situational awareness. The MRSN and AFHSC-GEIS systems have the largest international reach. They have been pivotal in identifying outbreaks within the military health care system and countries where personnel are stationed and also in assisting with response. The Walter Reed Army Institute of Research, home of the MRSN, is building on its success with anti-malarials. It supports testing of candidate compounds, standardization of models for testing, and characterization of mechanisms of resistance.

The Military Infectious Disease Research Program (MIDRP) has partnered with industry to create rapid diagnostics that are currently under FDA review. It is also supporting work on a novel antimicrobial delivery system, identification of human and bacterial biomarkers, and epidemiologic studies of soft-tissue infections. Dr. Smith believes that researchers are close to identifying biomarkers of drug resistance for malaria, which may contribute to understanding of antibiotic-resistant bacteria.

The Naval Medical Research Center is studying sepsis in austere environments with the aim of improving early recognition, diagnosis, and clinical management of patients with sepsis in resource-limited settings. The Joint Science and Technology Office (JSTO), Chemical and Biological Defense (CBD) program and the U.S. Army Medical Research Institute for Infectious Diseases are working with the four-nation Medical Countermeasures Consortium on developing detection assays for priority pathogens. The Medical Countermeasures Consortium is also working as part of the GHSA to develop consistent international standards to assess antibiotic resistance.

*Council Member Q&A*

Aileen M. Marty, M.D., FACP, asked what efforts are being made with legislators and legislative bodies in other countries to ensure that individuals have access to antimicrobials without a prescription. Ms. Poulton responded that the State Department works with countries on developing a regulatory framework for dealing with antibiotics to prevent resistance, which may or may not require legislation. Ms. Poulton said the USG encourages countries to ensure that the system, whether prescription-based or controlled, is adequate to achieve desired results. In many countries, individuals buy antibiotics over the counter, and the pharmacist determines whether antibiotics are needed. The solutions of the United States may not be applicable in other countries, said Ms. Poulton, so the USG is open to variations if the results are sufficient.

Angela Caliendo, M.D., Ph.D., FIDSA, noted that international collaboration is tricky for diagnostics. She asked how to get assays from overseas approved in the United States. Dr. Smith noted that many clinical trials are conducted overseas and the data collected in a rigorous format that meets FDA requirements. Luciana Borio, M.D., of FDA said there is no rule that precludes FDA from using data gathered in other countries for assessing the safety and efficacy of a product. However, study conditions vary, and some findings may not be applicable. Dr. Borio said FDA makes such decisions on a case-by-case basis.

Dr. Shryock asked about the status of an updated Codex Alimentarius. Dr. Kappes said there is discussion of reviving the task force that developed it. Dr. Clifford said he does not know of any now but USDA can reach out to FAO to learn more.

Dr. King said he was impressed with OIE's work with participatory disease surveillance and its ability to conduct assessments, which more than 100 countries have undergone. He would like to see a similar mechanism for public health, including animal and human health. He asked the panelists whether that was a good mechanism for harmonizing and strengthening efforts to combat antimicrobial resistance. Dr. Clifford agreed that the OIE approach was excellent. The GHSA offers a similar framework for evaluation, and the USG has agreed to evaluate it in that context. Dr. Clifford added that there has been discussion with OIE about including antimicrobial resistance in participatory disease surveillance, which would mean that the 180 members of OIE would be collecting antimicrobial use data.

Dr. Blaser noted that antibiotic use in other countries is often unregulated. He asked how to get data from such settings and what can be done to strengthen regulation. Unlike other drugs, inappropriate use of antibiotics affects other people broadly. Mr. Kolker said the WHO Global Action Plan discusses national strategies. In countries where antibiotics can be purchased over the counter, pharmacists can divert drugs for profit. Prescribing practices have raised barriers to international cooperation; for example, the U.S. and European countries have different requirements for prescription of veterinary drugs. There is a general sense of need for stewardship, regulation, and responsibility on the part of clinicians for appropriate use, because of the lack of diagnostics and the overuse of antibiotics. There is a need for national strategies for regulation and professional standards to prevent overuse, said Mr. Kolker.

Dr. Blaser added that farmers should also be involved in strategies to prevent overuse. Dr. Clifford observed that those countries that do not control antibiotic use probably do not have control over anything related to animal or human health, so their data likely is not trustworthy. Ms. Poulton said the State Department is working to improve regulatory oversight and raise public awareness about antibiotic use. Where there are economic limitations, trying to stretch out the use of antibiotics can create new problems; also, supply chain problems can interrupt treatment. Ms. Poulton said the USG is trying to approach the issue from every direction. Dr. Smith said other challenges are the quality of drugs and the availability of counterfeit drugs. Dr. Clifford said that in underdeveloped countries, there is much groundwork to do before spreading the word about the proper use of effective drugs.

Dr. Kester asked how the State Department supports other government agencies working internationally. Ms. Poulton said the State Department tries to provide a platform for other

agencies. There is regular discussion through an interagency committee to ensure awareness of what all the agencies are doing and to identify cross-cutting problems. The embassies provide a physical platform to support agencies working internationally. The State Department negotiates legal agreements, which are particularly important for research conduct and subsequent data exchange and licensing. Ms. Poulton said the USG is not always successful in negotiating with some governments, which affects the research and activities it can pursue.

Mr. Kolker said the paradigm of donor and recipient is in the past. Now, even developing countries want to establish partnerships. There are always efforts to develop synergy and to get the best science. Mr. Kolker said HHS can bring expertise, but the model of contracting for services is not as suitable for antimicrobial resistance as it is for other efforts, such as those under USAID.

## Public Comments

**Donald Stalons of Diatherix Laboratories at the HudsonAlpha Institute**, which is working with Life Technologies and Thermo Fisher Scientific, said the field is now in a position to consider molecular diagnostic technology to establish prevalence in bacterial antibiotic resistance. His laboratory has developed a machine-based technology that targets resistance to commonly used antibiotics in the health care system: beta lactams, quinolones, and macrolides. Mr. Stalons briefly described how the new technology works and said it has 99 percent specificity, with sensitivity yet to be determined. Data will be presented at an upcoming IDSA meeting. Mr. Stalons said he and his colleagues are excited about this new technology of exclusion rather than inclusion.

**Deborah Pasko of the American Society of Health-System Pharmacists** summarized efforts by her organization to combat antimicrobial resistance. At the White House Forum in June, the organization's chief executive officer committed to three things:

- Further development of interdisciplinary and pharmacy standardized metrics
- Continue efforts to expand antimicrobial stewardship efforts
- Foster telemedicine networks where underserved and/or under-resourced health organizations and communities exist

The organization will convene an expert panel in January 2016, primarily made up of members who are infectious disease experts plus three expert physicians. It will develop guidelines, policies, educational tools, and methods to accomplish its goals. The organization is collaborating with other organizations to ensure efficiency and avoid redundancy of effort.

**Kevin T. Kavanagh, M.D., M.S., of Health Watch USA**, said much of the research on which infectious disease policy is based is riddled with conflicts of interest, and even the editor of *The Lancet*, a premiere medical journal, has observed that much of the scientific literature may simply be untrue. Dr. Kavanagh recommended first that the PACCARB publish online its members' conflicts of interest for the past 4 years, along with those of their spouses and primary-degree relatives. Second, he said that firm recommendations are needed to make a meaningful impact; not making such recommendations because of conflicting evidence is unacceptable. Dr. Kavanagh pointed to reluctance to make recommendations about MRSA surveillance in surgical

patients, despite its positive effect, because of one conflicting study. Finally, Dr. Kavanagh suggested that development of any new antibiotics be tied to well-defined initiatives to prevent overuse and to mandatory public reporting of use. The drug industry almost universally tracks utilization data; thus, these data should be readily available, and the requirement should not be burdensome.

**Lisa McGiffert of Consumers Union**, said her organization has been working on the issue of antibiotic resistance since 2003 and supports the National Action Plan's human health goals. Ms. McGiffert called for instituting accountable antibiotic stewardship programs in all hospitals by the end of 2016. Such programs would be mandatory and include reporting of antibiotic use and drug-resistant infections to the NHSN, followed by reporting of the results to the public. Consumers Union brought infection reporting to the country and witnessed incredible actions stimulated by such mandates. The National Action Plan does not address the immediate needs of patients exposed to infection control breaches or outbreaks. Current infection reporting gives important information on trends and allows comparisons among hospitals. But at the time that superbugs are spreading in a hospital, patients and public health authorities rarely know about them. Ms. McGiffert said a national policy is needed that requires hospital to notify patients who have been exposed to a superbug through an outbreak or infection control breach and to notify patients coming in to the hospital during an outbreak. She described the case of an individual admitted during a MRSA outbreak who was infected and subsequently died. In addition, CDC and other public health officials should be notified about such outbreaks. Finally, Consumers Union urges the administration to eliminate the use of medically important antibiotics in healthy food animals not just for growth promotion but also for disease prevention.

**David Wallinga, M.D., M.P.A., of the Natural Resources Defense Council (NRDC)**, commended the National Action Plan for setting national goals to reduce inappropriate use of antibiotics in outpatient and inpatient settings. However, in animal production, where 70 percent of medically important antibiotics are sold, the National Action Plan does not give a hard target for phasing out use of these drugs for growth promotion. It also allows continued use of these drugs for disease prophylaxis. The NRDC urged the Advisory Council to recommend a hard target of reducing antibiotic use in animal agriculture by 50 percent by 2020. Furthermore, while there are mechanisms in place for health care facilities to report antibiotic use to a national network, data collection efforts are vague on the animal side. Under the veterinary feed directive, distributors of medicated feed are required to warehouse data, but FDA has not announced any plans to collect or analyze data on medicated feed. The NRDC urges FDA to analyze the data and report its findings to the PACCARB.

**Richard Wunderink, M.D., of the American Thoracic Society** strongly advocated for greater inclusion of the pulmonary and critical care community in the initiative to combat antibiotic-resistant bacteria. In particular antibiotic stewardship requires greater participation by primary care physicians caring for critically ill patients. Focusing on antibiotic use in intensive care units is important. However, gains made in treatment of infectious disease should not be sacrificed because of attempts to limit the use of specific antibiotics, including some new agents. There should be greater attention to new diagnostics for pneumonia. Dr. Wunderink said NIAID's new request for proposals on rapid diagnostics discouraged studying respiratory secretions. Pneumonia represents the most common and one of the most lethal sites of infection with

multidrug-resistant pathogens but does not often result in bacteremia. The need for better diagnostic platforms for pneumonia should be addressed in a separate request for proposals.

**Adriana Rosato, Ph.D., of the Houston Methodist Hospital Research Institute** expressed her enthusiasm for the PACCARB. She explained that she has been working in the field of antimicrobial resistance for 20 years and also represents some of the most vulnerable patients (e.g., those with cancer, cystic fibrosis, and HIV). She called for more research in these populations, looking, for example, at host-pathogen interactions and dynamics during antimicrobial resistance acquisition and also during treatment. She noted that those with immune-compromised systems are less responsive to antimicrobial treatment, and factors other than immunity may play a role. Dr. Rosato also said research indicates that those exposed to chemotherapy are predisposed to more resistance against antibiotics, which merits further investigation. More education of the community—including general physicians, health care workers, and the community at large—is needed before it is too late. Finally, Dr. Rosato suggested more investment in training. Infectious disease experts and clinical scientists receive training currently, but few programs involve Ph.D.'s. All can contribute to the understanding of antimicrobial resistance.

**Tharini Sathiamoorthy of AdvaMedDx** said diagnostic manufacturers are developing critical tests to identify, monitor, and track appropriate implementation of appropriate infection control procedures. While AdvaMedDx commends the administration for establishing the PACCARB, it is disappointed that the Council does not include any members with a background in the development, commercialization, or global distribution of diagnostic tests. A commercial perspective is critical to leverage the private sector's capability to distribute new tests and to understand how to address technological and commercial barriers that may exist. AdvaMedDx requests that the administration rectify this critical oversight by appointing an additional Council member with commercial diagnostic manufacturing perspective and expertise.

**Amanda Jezek of the IDSA**, said her organization has been sounding the alarm for over a decade about the public health crisis of antibiotic resistance that is sickening and killing patients and compromising the ability to practice medicine. The IDSA has long promoted a set of comprehensive, multipronged policy solutions to address this problem, and the National Action Plan holds great promise for advancing these solutions if adequate funding is provided. The IDSA pledges to support the PACCARB and all federal partners in their important work to combat antibiotic resistance. Infectious disease physicians are at the forefront of the battle, caring for patients, leading stewardship programs, running clinical trials, and advancing public health efforts. Ms. Jezek said cooperation is needed to achieve critical policy and cultural changes. To assist, the IDSA has convened the U.S. Stakeholder Forum on Antimicrobial Resistance, which includes more than 110 partner organizations representing health care professionals, researchers, patients, public health, industry, hospitals, and other collaborators across the human and animal health spectrum. This group educates partners and policymakers about antibiotic resistance policy issues and mobilizes partners for advocacy.

**John Boyce of J.M. Boyce Consulting, LLC**, said he was the lead coauthor of CDC's guidelines for hand hygiene in health care and a member of a group that assisted with WHO's hand hygiene guideline. He noted that the Council's discussion today described many initiatives, strategies, and collaborations underway but included almost no discussion of hand hygiene,



which is widely considered one of the most effective strategies for preventing the spread of resistant organisms from one person to another. Dr. Boyce encouraged the Council to include promotion of improved hand hygiene practices as one strategy to prevent the spread of infection.

The PACCARB members reviewed additional comments submitted in writing.

### **Next Steps and Adjournment**

Dr. Blaser thanked Co-Chair Dr. King, all of the speakers, and the other federal agency representatives involved in the task force. He thanked the Council Members for their patience and their enthusiasm for the topic. Dr. Blaser thanked Dr. Gellin and his team, especially Jomana F. Musmar, M.S., Ph.D.c, Sean Andrews, M.P.H., Marcus Manning, and Tiffany Archuleta. Finally, he thanked the audience for attending.

Dr. Blaser said the Council Members have a lot of material to digest. The next step is to form working groups, starting with one working group for each of the five goals of the National Action Plan. The initial steps of the working groups will be to define the key questions for federal government partners. After that, the PACCARB will determine the kinds of outside expertise and input it needs to enhance its deliberations. The next meeting will be scheduled once the PACCARB has accomplished these steps. When determined, the date of the next meeting will be posted online.

With no further discussion or business brought before the PACCARB, Dr. Blaser adjourned the meeting at 5:11 p.m.

I hereby certify that to the best of my knowledge, the foregoing minutes of the proceedings are accurate and complete.

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Martin J. Blaser, M.D., Chair  
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

# **Appendix A: Charter: Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria**

## **CHARTER**

### **PRESIDENTIAL ADVISORY COUNCIL ON COMBATING ANTIBIOTIC-RESISTANT BACTERIA**

#### **Authority**

Executive Order 13676, dated September 18, 2014, requires establishment of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (Advisory Council). Activities of the Advisory Council are governed by the provisions of Public Law 92-463, as amended (5 U.S.C. App.), which sets forth standards for the formation and use of federal advisory committees.

#### **Objectives and Scope of Activities**

Executive Order 13676 directs the Secretary of Health and Human Services (Secretary) to establish the Advisory Council in consultation with the Secretaries of Defense and Agriculture. The Advisory Council will provide advice, information, and recommendations to the Secretary regarding programs and policies intended to support and evaluate the implementation of Executive Order 13676, including the National Strategy for Combating Antibiotic-Resistant Bacteria (Strategy) and the National Action Plan for Combating Antibiotic-Resistant Bacteria (Action Plan). The Advisory Council shall function solely for advisory purposes.

#### **Description of Duties**

In carrying out its mission, the Advisory Council will provide advice, information, and recommendations to the Secretary regarding programs and policies intended to:

1. Preserve the effectiveness of antibiotics by optimizing their use;
2. Advance research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship;
3. Strengthen surveillance of antibiotic-resistant bacterial infections;
4. Prevent the transmission of antibiotic-resistant bacterial infections;
5. Advance the development of rapid point-of-care and agricultural diagnostics;

*Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria*

6. Further research on new treatments for bacterial infections;
7. Develop alternatives to antibiotics for agricultural purposes;
8. Maximize the dissemination of up-to-date information on the appropriate and proper use of antibiotics to the general public and human and animal healthcare providers; and
9. Improve international coordination of efforts to combat antibiotic resistance.

**Agency or Official to Whom the Committee Reports**

As stipulated in Executive Order 13676, the Advisory Council provides advice, information, and recommendations to the Secretary. The Secretary will provide the President with all written reports created by the Advisory Council.

**Support**

To the extent permitted by law and subject to the availability of appropriations, the Department of Health and Human Services (HHS) shall provide the Advisory Council with such funds and support as may be necessary for the performance of its functions. Management and support services provided to the Advisory Council will be the responsibility of the Office of the Assistant Secretary for Health (OASH), which is a coordinating and program office within the Office of the Secretary.

To the extent permitted by law, the agencies that comprise the Task Force for Combating Antibiotic-Resistant Bacteria shall provide the Advisory Council with such information as it may require for purposes of carrying out its functions.

**Estimated Annual Operating Costs and Staff Years**

The estimated annual cost for operating the Advisory Council, including compensation and travel expenses for members, but excluding staff support is \$472,000. The estimate for annual person years of staff support required is 5.0, at an estimated annual cost of \$654,017.

**Designated Federal Officer**

The Assistant Secretary for Health (ASH), in consultation with the Secretary, will select the Designated Federal Officer (DFO) from among full-time or permanent part-time staff within OASH or another organizational component within the HHS, who have knowledge of the subject matter and skills and experience necessary to manage the Advisory Council. The ASH may appoint an Alternate DFO, who will carry out the assigned duties in the event that the DFO cannot fulfill the assigned responsibilities for the Advisory Council. In the absence of a DFO

*Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria*

or Alternate DFO, the ASH will temporarily appoint one or more permanent full-time or part-time program staff to carry out the assigned duties.

The DFO will schedule and approve all meetings of the Advisory Council and of its respective subcommittees. The DFO will prepare and approve all meeting agendas. The DFO may collaborate with the Advisory Council Chair in this activity, and when deemed appropriate, with chairs of any existing subcommittees that have been established by the Advisory Council. The DFO, Alternate DFO, or designee will attend all meetings of the Advisory Council and all meetings of any subcommittees/working groups that have been assembled to assist the Advisory Council. The DFO has authority to adjourn meetings, when it is determined to be in the public interest, and the DFO can be directed by the Secretary or designee to chair meetings of the Advisory Council.

**Estimated Number and Frequency of Meetings**

The Advisory Council will meet, at a minimum, two times per fiscal year depending on the availability of funds. Meetings will be open to the public, except as determined otherwise by the Secretary, or other official to whom authority has been delegated, in accordance with guidelines under Government in the Sunshine Act, 5 U.S.C. 552b(c). Notice of all meetings will be provided to the public in accordance with the Federal Advisory Committee Act (FACA), Public Law 92-463, as amended (5 U.S.C. App.). Meetings will be conducted and records of the proceedings will be kept, as required by applicable laws and Departmental policies. A quorum is required for the Advisory Council to meet to conduct business. A quorum will consist of a majority of the Advisory Council's voting members.

When the Secretary or designee determines that a meeting will be closed or partially closed to the public, in accordance with stipulations of Government in the Sunshine Act, 5 U.S.C. 552b(c), then a report will be prepared by the DFO that includes, at a minimum, a list of the members and their business addresses, the Advisory Council's functions, date and place of the meeting, and a summary of the Advisory Council's activities and recommendations made during the fiscal year. A copy of the report will be provided to the Department Committee Management Officer.

**Duration**

Continuing. The Advisory Council was established by an Executive Order; no specific end date was established for the Advisory Council to operate.

**Termination**

Unless renewed by appropriate action prior to its expiration, the charter for the Advisory Council will expire two years from the date it is filed.

## **Membership and Designation**

The Advisory Council will consist of not more than 30 members, including the voting and non-voting members and the Chair and Vice Chair. The Secretary will designate the Chair and Vice Chair from among the voting public members of the Advisory Council who have demonstrated ability both to lead the work of similar bodies and to work effectively in partnership with federal agencies and partner organizations.

***Voting Members.*** There will public voting members selected from individuals who are engaged in research on, or implementation of, interventions regarding efforts to preserve the effectiveness of antibiotics by optimizing their use; advance research to develop improved methods for combating antibiotic resistance and conducting antibiotic stewardship; strengthen surveillance of antibiotic-resistant bacterial infections; prevent the transmission of antibiotic-resistant bacterial infections; advance the development of rapid point-of-care and agricultural diagnostics; further research on new treatments for bacterial infections; develop alternatives to antibiotics for agricultural purposes; maximize the dissemination of up-to-date information on the appropriate and proper use of antibiotics to the general public and human and animal healthcare providers; and improve international coordination of efforts to combat antibiotic resistance.

The public voting members will represent balanced points of view from human biomedical, public health, and agricultural fields to include surveillance of antibiotic-resistant infections, prevention and/or interruption of the spread of antibiotic-resistant threats, or development of rapid diagnostics and novel treatments. The public voting members may be physicians, veterinarians, epidemiologists, microbiologists, or other health care professionals (e.g., nurses, pharmacists, others); individuals who have expertise and experience as consumer or patient advocates concerned with antibiotic resistance, or in the fields of agriculture and pharmaceuticals; and they also may be from State or local health agencies or public health organizations. The voting public members will be appointed by the Secretary, in consultation with the Secretaries of Defense and Agriculture. All public voting members will be classified as special Government employees (SGEs).

***Ex-officio Members (non-voting).*** The Advisory Council will include members selected to represent various federal agencies, including HHS, DoD, and USDA, that are involved in the development, testing, licensing, production, procurement, distribution, and/or use of antibiotics and/or antibiotic research. The federal *ex-officio* members shall possess the knowledge, skills, experience, and expertise necessary to generate informed and intelligent recommendations with respect to the issues mandated by Executive Order 13676. Federal agencies will be invited to participate as non-voting *ex-officio* members of the Advisory Council, as it is deemed necessary by the Secretary, in consultation with the Secretaries of Defense and Agriculture, to accomplish the mission the Advisory Council.

***Liaison Representatives (non-voting).*** The Advisory Council structure also may include non-voting liaison representatives from organizations and/or interest groups that have involvement in the development, testing, licensing, production, procurement, distribution, and/or use of antibiotics and/or antibiotic research. Individuals from among the following sectors may be invited to serve as non-voting liaison representatives:

- Professional organizations representing: infectious disease; epidemiology; infection control; physicians; nurses; pharmacists; microbiologists; veterinarians
- Public health organizations representing laboratories, health officials, or epidemiologists (state/territorial, county, or local)
- Organizations advocating for patients and consumers
- Organizations representing state departments of agriculture
- Hospitals
- Foundations with an interest in antibiotic resistance and promoting antibiotic stewardship
- National Preparedness and Response Science Board
- Pharmaceutical industry – human health
- Pharmaceutical industry – animal health
- Vaccines
- Food producer (livestock)
- Food producer (poultry)
- Food producer (seafood)
- *In vitro* diagnostics
- Food retailer
- Food processor
- Animal feed producers
- Farm bio-security

Invitations may be extended to other organizations and/or interest groups to participate as non-voting liaison representatives, as it is deemed necessary by the Secretary or designee to accomplish the established mission of the Advisory Council.

***Terms and Compensation.*** The public voting and non-voting liaison representative members will be appointed to serve for overlapping terms of up to four years. Any member who is appointed to fill the vacancy of an unexpired term will be appointed to serve for the remainder of that term. The Chair and Vice Chair will be appointed to serve for three years, unless otherwise specified. Terms of more than two years are contingent upon renewal of the Advisory Council charter by appropriate action prior to its expiration. A member may serve after the expiration of their term until their successor has taken office, but no longer than 180 days.

Pursuant to an advance written agreement, the public voting members shall receive no stipend from the federal government for the services they perform during their tenure on the Advisory

*Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria*

Council. However, the public voting members are entitled to receive per diem and reimbursement for travel expenses incurred for attending meetings of the Advisory Council, as authorized by 5 U.S.C.

Sec. 5703, as amended, for persons who are employed intermittently in the Government service. The non-voting liaison representatives may be allowed to receive per diem and any applicable expenses for travel that is performed to attend meetings of the Advisory Council in accordance with federal travel regulations.

**Subcommittees/Working Groups**

With approval or recommendation of the Secretary or designee, the Advisory Council may establish standing and *ad hoc* subcommittees and/or working groups to provide assistance for carrying out its function. These subgroups may consist of members of the Advisory Council, as well as other individuals (federal and non-federal) who are concerned and knowledgeable about antibiotic-resistant bacteria and other topics pertaining to the Advisory Council mission.

The Department Committee Management Officer will be notified upon establishment of each subcommittee or working group, and will be provided information on its name, membership, function, and estimated frequency of meetings. All reports and recommendations of a subcommittee or workgroup must be reported back to the full Advisory Council for action. No activity of a subcommittee or working group can be given directly to the Secretary without being provided for discussion by the full Advisory Council.

**Recordkeeping**

Records of the Advisory Council and the respective subcommittees or working groups will be handled in accordance with General Schedule 26, Item 2 or other approved agency records disposition schedule. These records will be available for public inspection and copying, subject to the Freedom of Information Act, 5 U.S.C. 552.

## **Appendix B: Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) Member Roll-Call, September 29, 2015**

### **PACCARB Voting Members**

Martin J. Blaser, M.D., Chair (present)  
Michael D. Apley, D.V.M., Ph.D., DACVCP (present)  
Helen W. Boucher, M.D., FIDSA, FACP (present)  
Angela Caliendo, M.D., Ph.D., FIDSA (present)  
Alicia R. Cole (present)  
Sara E. Cosgrove, M.D., M.S. (present)  
Lonnie J. King, D.V.M., M.S., M.P.A., ACVPM, Vice Chair (present)  
Peter Robert Davies, B.V.Sc., Ph.D. (present)  
Kent E. Kester, M.D., FACP, FIDSA, FASTMH (present)  
Ramanan Laxminarayan, Ph.D., M.P.H. (present)  
Aileen M. Marty, M.D., FACP (present)  
John H. Rex, M.D. (present)  
Thomas R. Shryock, Ph.D. (present)  
Randall Singer, D.V.M., M.P.V.M., Ph.D. (present)  
Robert A. Weinstein, M.D. (present)

### **Organizational Liaisons**

Animal Health Institute: Richard Carnevale, V.M.D. (present)  
Association of State and Territorial Health Officials: Jewel Mullen, M.D., M.P.H., M.P.A. (**not present**)  
National Association of Directors of Nursing Administration in Long Term Care: Sherrie Dornberger, R.N., CDONA, GDCN, CDP, CADDCT, FACDONA (present)  
National Pork Producers Council: Elizabeth Allen Wagstrom, D.V.M., M.S. (present)  
The Pew Charitable Trusts: Elizabeth Jungman, J.D., M.P.H. (present)

### **Ex Officios**

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Dennis M. Dixon, Ph.D. (present)  
Chief, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Richard J. Hatchett, M.D. (present)  
Chief Medical Officer and Deputy Director, Biomedical Advanced Research and Development Authority, Assistant Secretary for Preparedness and Response

Shari Ling, M.D. (present)  
Deputy Chief Medical Officer, Centers for Medicare and Medicaid Services



Peter Lurie, M.D. (present)  
Associate Commissioner for Public Health Strategy and Analysis, Food and Drug Administration

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David Goldman, M.D. (present)  
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## **Appendix C: Roster, Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria**

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## Glossary of Abbreviations

Abbreviation	Description
AFHSC-GEIS	Armed Forces Health Surveillance Center Global Emerging Infections Surveillance and Response System
AHRQ	Agency for Healthcare Research and Quality
APHIS	Animal and Plant Health Inspection Service
ARS	Agricultural Research Service
ASPR	Assistant Secretary for Preparedness and Response
AST	antibiotic susceptibility testing
ASTHO	Association of State and Territorial Health Officials
BARDA	Biomedical Advanced Research and Development Authority
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare and Medicaid Services
CRE	carbapenem-resistant <i>Enterobacteriaceae</i>
CVM	Center for Veterinary Medicine
DoD	U. S. Department of Defense
EMR	electronic medical record
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
FSIS	Food Safety and Inspection Service
GAIN	Generating Antibiotic Incentives Now (Act)
GHSA	Global Health Security Agenda
FY	fiscal year
HAI	health-care-associated infection
HHS	Department of Health and Human Services
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IICAB	Institute for International Cooperation in Animal Biologics
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MRSN	Multidrug-Resistant Organism Repository and Surveillance Network
NAHLN	National Animal Health Laboratory Network
NAHMS	National Animal Health Monitoring System
NARMS	National Antimicrobial Resistance Monitoring System
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NIFA	National Institute of Food and Agriculture
NIH	National Institutes of Health
NQF	National Quality Forum
NRDC	Natural Resources Defense Council

<b>Abbreviation</b>	<b>Description</b>
NVPO	National Vaccine Program Office
OIE	World Organization for Animal Health
OSTP	White House Office of Science and Technology Policy
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PCAST	President's Council of Advisors on Science and Technology
PKPD	pharmacokinetics/pharmacodynamics
Q&A	questions and answers
QIDP	qualified infectious disease product
R&D	research and development
TATFAR	Transatlantic Task Force on Antimicrobial Resistance
USAID	U.S. Agency for International Development
USDA	U.S. Department of Agriculture
USG	U.S. government
VA	U.S. Department of Veterans Affairs
Vet-LIRN	Veterinary Laboratory Investigation and Response Network
VFD	Veterinary Feed Directive
VHA	Veterans Health Administration
VICH	International Cooperation on Harmonization of Technical Requirements for Veterinary Medicinal Products
WHO	World Health Organization