

RECOMMENDATIONS FOR
INCENTIVIZING THE DEVELOPMENT
OF THERAPEUTICS, DIAGNOSTICS,
AND VACCINES TO COMBAT
ANTIBIOTIC-RESISTANCE

WORKING GROUP - DRAFT

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EXECUTIVE SUMMARY

The spread of antimicrobial resistance (AMR) is one of the most pressing public health problems facing the globe today. World leaders have recently acknowledged the growing threat of AMR; for example, the United Nations held a high-level meeting on AMR in September 2016, and the Group of 20 (G20) released a declaration on combatting AMR in July 2017. Without interventions to curb the spread of AMR, it has been projected that by 2050, resistant infections will kill more people worldwide than cancer¹ and cause global economic damage on par with the financial crisis of 2008². The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) was established in 2015 in consultation with the Secretaries of Defense, Agriculture, and Health and Human Services as part of a coordinated effort by the U.S. government to respond to this threat. In its 2015 report, *Initial Assessments of the National Action Plan for Combating Antibiotic-Resistant Bacteria*, PACCARB suggested that the current economic model is insufficient to ensure the availability of products and resources to fight AMR. Consequently, the PACCARB agreed to propose recommendations for incentivizing the development of new products to reduce the spread of AMR for both humans and animals.

Accordingly, the PACCARB established three working groups (WGs) on incentives—for vaccines, diagnostics, and therapeutics/anti-infectives—composed of council members and federal official subject matter experts in both human and animal domains. This report presents the WGs’ findings on the critical issues that can hinder the development of products to reduce the spread of AMR and recommendations for incentives on how to address these barriers. To help organize and structure its findings, the WGs developed a framework, categorizing issues according to four broad buckets: economic, research and development, regulatory, and behavioral. The PACCARB acknowledges that prevention extends far beyond vaccination to broader behavioral and structural interventions. However, for this report, prevention is only discussed in terms of the development and use of vaccines.

Recommendations

Across both human and animal domains, the WGs identified 46 critical issues that hinder the development of new and improved products and proposed 64 recommendations to address them. PACCARB selected its top recommendations by estimating which could have the greatest impact on product development. These top recommendations are presented in the figure following this page. A detailed explanation of each recommendation is included in the body of the report.

¹ Jim O’Neill, Review on Antimicrobial Resistance, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations* (Review on Antimicrobial Resistance, 2016), http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

² World Bank Group. *Drug-resistant infections: a threat to our economic future (Vol. 2): Final Report*. (World Bank Group, 2017) <http://documents.worldbank.org/curated/en/323311493396993758/final-report>

Human Health

Incentives to Develop

Animal Health



Provide additional funding for the development of new product pipelines for vaccines that prevent viral or bacterial syndromes that drive antibiotic use



Optimize the interactions among sponsors, regulatory agencies (such as FDA), and use policy committees (e.g., the ACIP)



Incentivize the uptake of vaccines by influencing behavior, such as reimbursement to ensure “first-dollar coverage”



Vaccines

Develop and fund a National Policy and Innovation Institute under USDA whose main functions will include the following:



Support basic research on immunology across species for the development of vaccines



Include the development of a concomitant rapid AST as part of any new antibiotic funding (or funding for new antibiotics)



Provide financial support for diagnostic manufacturers to bring new tests to market



Continue funding for clinical trials networks with common rules or shared IRBs



Diagnostics



Promote educational programs for veterinarians on the use and interpretation of diagnostic tests



Develop new economic models (pull incentives) for therapies to support the currently available push incentives



Therapeutics / Anti-Infectives



Provide resources to conduct, evaluate, and create a database of efficacy studies of alternative products

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INTRODUCTION

The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria's (PACCARB's) first report, *Initial Assessments of the National Action Plan for Combating Antibiotic-Resistant Bacteria*,³ evaluated the U.S. government's (USG's) progress towards reducing and preventing the spread of antimicrobial resistance (AMR). In that report, the Council suggested that the current economic model is insufficient to ensure the availability of products and resources to fight AMR. Consequently, the PACCARB agreed to propose ideas for incentivizing the development of therapeutics, diagnostics, and vaccines, for both humans and animals, while maximizing the return on investment (ROI) and encouraging appropriate stewardship and access to products.

For this task, the PACCARB established three working groups (WGs) composed of council members and federal official subject matter experts in both human and animal domains to address incentives for developing vaccines, diagnostics, and therapeutics/anti-infectives. To help organize and structure their findings, the WGs developed a framework, categorizing issues according to four broad types: economic, research and development (R&D), regulatory, and behavioral. For the purposes of this report, the categories are defined as follows:

- **Economic:** Issues that influence the ROI to companies or food animal producers regarding product development or use
- **R&D:** Issues related to discovery research and the development process
- **Regulatory:** Issues related to the federal regulatory processes that influence the development or modification of a product, ranging from basic research through studies that meet approval criteria
- **Behavioral:** Issues related to the behavior of consumers, providers, end-users, or companies relative to product use or development

The WGs recognize that many of the issues identified have overlapping implications that could be addressed under more than one category, and these are acknowledged in the text. This report is divided into two sections: human health and animal health. A common theme that links the human and animal sections—and that informs the task of the WGs in general—is the concept of One Health, which could be defined as the interconnectedness of the health of humans, animals, plants, and the environment and the need for an integrated, collaborative approach across these domains. For example, for novel antibiotics that are not suitable for human use, the potential for development for animal use might be considered. As recognized by many, AMR epitomizes the concept of One Health, as the genes that confer resistance to antibiotics; the organisms harboring these genes; and the pressures that enhance the evolution, spread, and persistence of these genes and organisms are present in all domains. From a One Health perspective, a consistent concern about AMR is the disproportionately lower allocation of funding for research in animal health, crop health, and environmental health when compared with human health. To adequately address the problem of AMR as a whole, additional resources should be allocated for AMR research and interventions in the domains of agriculture and environmental health.

Before attempting to generate recommendations, the WGs sought to better understand the primary issues driving the lack of investment in and corresponding development of vaccines, diagnostics, and therapeutics/anti-infectives. This final report describes the issues identified by the WGs and provides recommendations to the Secretary of the Department of Health and Human Services (HHS) for possible

³ PACCARB, *Initial Assessments of the National Action Plan for Combating Antibiotic-Resistant Bacteria* (U.S. Department of Health and Human Services, 2016), <https://www.hhs.gov/sites/default/files/paccarb-final-report-03312016.pdf>

ways the USG could stimulate innovation and overcome identified barriers, with the ultimate goal of minimizing and containing AMR in humans and animals.

Governmental and nongovernmental agencies, including some at the international level, have put a lot of effort into investigating the challenges of developing products to combat AMR. The WGs reviewed publications, reports, initiatives, and legislation (both pending and passed) by individuals and organizations. The WGs acknowledge the advances and work currently in progress by the USG, notably by the Biomedical Advanced Research and Development Authority (BARDA), the Centers for Disease Control and Prevention (CDC), the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Department of Agriculture (USDA). The WGs also recognize the contributions of several professional organizations and consortia that have put forth recommendations for incentivizing early R&D across the pipeline of product development, particularly the following:

- Chatham House⁴
- Duke University's Margolis Center for Health Policy⁵
- Wellcome Trust, both via its direct activities and its support for the United Kingdom AMR Review/O'Neil Group⁶
- Driving Re-Investment in R&D and Responsible Antibiotic Use (DRIVE-AB) consortium⁷
- Pew Charitable Trust, Infectious Diseases Society of America (IDSA), and the Pharmaceutical Research and Manufacturers of America (PhRMA)⁸

In addition, the WGs hosted a series of meetings, including a public meeting May 4, 2017, dedicated to the topic of incentives. They also held several conference calls with subject matter experts on various topics.

The WGs consisted of animal health and human health experts, and ideas were shared across domains. However, for organizational purposes, this report addresses human health and animal health in separate sections. Each section describes in brief the issues identified by the WGs regarding the development of vaccines, diagnostics, and therapeutics/alternatives, and presents corresponding recommendations to address them. Additionally, each WG member reviewed the report as a whole and provided feedback and input on the final document.

⁴ Chatham House Working Group on New Antibiotic Business Models, *Chatham House Report: Towards a New Global Business Model for Antibiotics: Delinking Revenues from Sales* (Chatham House, 2015), https://www.chathamhouse.org/sites/files/chathamhouse/field/field_document/20151009NewBusinessModelAntibioticsCliftGopinathanMorelOuttersonRottingenSo.pdf

⁵ Duke-Margolis Center for Health Policy, *Value-Based Strategies for Encouraging New Development of Antimicrobial Drugs* (Duke-Margolis Center for Health Policy, 2017), https://healthpolicy.duke.edu/sites/default/files/atoms/files/value-based_strategies_for_encouraging_new_development_of_antimicrobial_drugs.pdf

⁶ Jim O'Neill, Review on Antimicrobial Resistance, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations* (Review on Antimicrobial Resistance, 2016), http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

⁷ Driving Re-Investment in R&D and Responsible Antibiotic Use (DRIVE-AB), *Incentives to Stimulate Antibiotic Innovation: The Preliminary Findings of DRIVE-AB* (DRIVE-AB, 2016), <http://drive-ab.eu/wp-content/uploads/2016/06/WP2-Prereading-FINAL.pdf>

⁸ Pew Health Group, IDSA, PhRMA, *Reviving the Pipeline of Life-Saving Antibiotics: Exploring Solutions to Spur Innovation* (Conference proceedings, September 22, 2011), http://www.pewtrusts.org/~media/legacy/uploadedfiles/phg/content_level_pages/issue_briefs/AIPPipelineProceedings9webpdf.pdf

SECTION I. HUMAN HEALTH

On average, the cost of development of a human vaccine or therapeutic ranges from \$300 million to more than \$1 billion and can take more than 12 years from the start of basic research to delivery to the consumer. A variety of financial and regulatory incentives are needed to address the lack of development of products and undervaluation of existing products to combat antibiotic⁹ resistance. Therefore, investment from both public and private entities is required to fill this gap. The market forces that affect vaccines, diagnostics, and therapeutics are very different and thus require individualized approaches to spur investment. Examples of such measures can include national legislation, funding commitments, fast-track regulatory pathways, investment in outcomes research, reforms to the reimbursement system, and development of novel business models.

Furthermore, most previously published reports recommend some sort of combination of “push” incentives (which provide direct support to underwrite the cost of development) and “pull” incentives (which create market demand or reward successful development). Push incentives include grants, contracts, and tax credits during the development phase, while pull incentives include prizes, market exclusivity, and downstream financial rewards that come into play after approval of the respective product. There are pros and cons of each approach, and they are not mutually exclusive. In addition, how these incentives might be applied to vaccines, therapeutics, and diagnostics varies. Therefore, several types of push and pull incentives are discussed in the following sections on human health. Many groups have previously made economic recommendations primarily focused on antimicrobials, including the recent work conducted by the Duke-Margolis Advisory Group on U.S. payment models for effective antimicrobial development and use. Therefore, the section of this report on human therapeutics is more developed than the other sections, as it reiterates many of the incentive ideas proposed by others before PACCARB’s work.

1. Incentives for Vaccines for Human Use

Vaccines for humans can directly target bacterial pathogens that have developed or have the potential to develop AMR. The protective immune responses to bacterial vaccines do not discriminate between antibiotic-susceptible and antibiotic-resistant strains, nor do they generate resistance to the vaccine. This outcome was demonstrated by the introduction of *Haemophilus influenzae* type B and pneumococcal vaccines, which dramatically reduced infections caused by both antibiotic-susceptible and antibiotic-resistant strains. Vaccines that target viral pathogens can address AMR directly by reducing the incidence of secondary bacterial infections and indirectly by reducing infections that cause syndromes often treated inappropriately with antibiotics. Such vaccines are already available for mass immunization against influenza, measles, respiratory syncytial virus (RSV), rotavirus, and varicella. Achieving high coverage rates with these viral vaccines could have a significant impact on reducing AMR.

Despite their demonstrated public health and financial benefits to society, the development and use of vaccines face a variety of behavioral, economic, and regulatory challenges that reduce the willingness of companies to fund R&D efforts. Manufacturers lack incentives to develop vaccines against new pathogen targets or to improve existing vaccines, particularly for low-volume/high-severity or high volume/low-severity conditions for which AMR may play a major role in morbidity, mortality, and health care costs. Vaccines and other AMR-relevant prophylactic interventions (e.g., monoclonal antibodies) should be

⁹ In this report, the term “antibiotics” refers to antibacterials, although similar considerations apply to antifungals.

considered for inclusion in legislation that incentivizes the development of AMR products. The GAIN¹⁰ Act and current drafts of the proposed DISARM¹¹ and READI¹² Acts do not include incentives for prophylactic interventions. The exclusion of incentives for preventive AMR products is a further barrier to development of vaccines that may reduce the burden of AMR pathogens.

1.1 Economic

Issue Statement 1: Federal and nonfederal stakeholders lack a common understanding about the current and potential economic value and societal impact of vaccines that can reduce AMR.

While widespread recognition of the value of vaccines for the pediatric population results in continued public support for ensuring the delivery of these vaccines to all children under the Vaccines for Children program, the understanding of their relevance in adults is not as well established among stakeholders. Stakeholders do not recognize or appreciate the value of vaccines with respect to reducing the demand for antibiotics, and no incentives or specific programs are in place to support analyses of this value. An essential aspect of properly positioning vaccines as an element of a larger U.S. response against AMR is to generate data that clearly documents how vaccines—existing or to-be-developed—can reduce AMR-related morbidity and mortality and the associated significant economic impact. Such data can then inform supportable research, investment, and incentive strategies, potentially reducing the development risk associated with small market-focused vaccines.

The WG recommends the following:

- **Analyses on the cost and societal impacts associated with new vaccine development and administration in the AMR arena developed via a multi-agency process that involves at least CDC, the Centers for Medicare and Medicaid Services (CMS), and the Treasury Department, in partnership with industry and public health stakeholders.** Mathematical modeling efforts should be expanded to demonstrate the health and economic benefits of vaccines with respect to AMR. Data on the health and economic benefits of new vaccines directed against pathogens associated with AMR can be used to support price levels that reflect the value of the vaccines to society and to provide an economic incentive to companies and investors. Analyses should assess the potential AMR impact of all licensed vaccines, because the complications of vaccine-preventable diseases often receive antibiotic treatment (appropriately or inappropriately).

Issue Statement 2: There is limited funding for developing infectious disease vaccines, in particular for those targeting AMR-related pathogens.

Vaccines can help reduce AMR by preventing syndromes caused by viruses or bacteria that drive use of antibiotics. Only large pharmaceutical companies can absorb the risks and costs of sustained, end-to-end development and deployment of infectious disease vaccines. Smaller companies and other organizations find it exceedingly difficult to raise sufficient, sustained capital to develop needed vaccines, especially

¹⁰ *Generating Antibiotic Incentives Now Act*, Title VIII of the *Food and Drug Administration Safety and Innovation Act*, Public Law 112–144, U.S. Statutes at Large 126 (2012): 993.

¹¹ *Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms Act*, H.R. 512, 114th Congress, 1st Session, <https://www.gpo.gov/fdsys/pkg/BILLS-114hr512ih/content-detail.html>

¹² *Reinvigorating Antibiotic and Diagnostic Innovation Act*, H.R. 1840, 115th Congress, 1st Session, <https://www.gpo.gov/fdsys/search/pagedetails.action?st=Reinvigorating+Antibiotic+and+Diagnostic+Innovation+Act&packageId=BILLS-115hr1840ih&fromState=>

those utilizing novel technologies or focused on new targets and for which the market may be limited. The lack of capital means that vaccine research by academics, government agencies, and nongovernmental organizations may not be translated to smaller biotechnology companies, leading to further erosion of the early-stage pipeline of vaccines that may specifically target AMR pathogens or failure of these early pipeline efforts to progress or both.

The WG recommends the following:

- **An expanded range of incentives to encourage development of vaccines that could reduce AMR by preventing the syndromes caused by bacteria and viruses that lead to antibiotic use.** Push incentives include grants, contracts, and public-private partnerships (e.g., NIH, the Department of Defense [DoD], BARDA, and the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator [CARB-X]) and transferable tax credits for vaccine development (e.g., the READI Act). Ideally, and where appropriate, these incentives should be coordinated across federal agencies to reduce programmatic and funding redundancies. Pull incentives include the development of transferable market exclusivity, expansion of the GAIN Act to include vaccines, and expansion of Prescription Drug User Fee Act (PDUFA) fee waivers for small companies developing vaccines. In particular, FDA should explore the feasibility of expanding current incentive programs (e.g., priority review vouchers) to apply to any vaccine that may have a positive impact on reducing AMR and should include consideration of information related to AMR benefits of vaccines in licensing packages. Expansion of programs may include additional enabling via legislative action. (*See also R&D Issue Statement 2.*)

1.2 Research and Development

Issue Statement 1: There are insufficient epidemiological data on antibiotic use for infections caused by pathogens currently or potentially preventable through vaccination.

Additional understanding is needed about how much inappropriate use of antibiotics is attributed to treating vaccine-preventable diseases. Improved data from surveillance (e.g., infectious disease epidemiology and antibiotic prescribing data) can inform vaccine development and deployment strategies by enhancing the use of vaccines.

The WG recommends the following:

- **Expanded funding for surveillance by CDC (e.g., Emerging Infections Program and National Healthcare Safety Network) and CMS to measure antibiotic use for infections that could be prevented or reduced by vaccination to assess the impact or potential impact of prevention through immunization, either by existing or to-be-developed vaccines.**

Issue Statement 2: The clinical-stage pipeline for vaccines targeted specifically against bacterial pathogens associated with AMR is weak.

Vaccine development for infectious disease is a form of public health R&D. In general, most vaccines focus on large populations. Vaccines specifically for bacterial pathogens that have high rates of AMR often have a more limited target population, making it more of a challenge for a developer to commit to a sustained development effort. Specifically, vaccine effectiveness trials are conducted in small populations that may be difficult to identify (e.g., *Staphylococcus aureus* vaccine trials in elective surgery patients or *Clostridium difficile* vaccine trials in patients at high risk). Vaccine developers may find it challenging to commit (or remain committed) to such efforts because of the significant costs and anticipated very limited

(or no) ROI, although the public health value of these “niche” vaccines remains important (analogous to the treatment of orphan diseases). Effective approaches to enhance the R&D pipelines of vaccine developers, in both government and private industry, will be an important aspect of the response to reducing AMR.

The WG recommends the following:

- **Focused financial incentives to encourage the development of vaccines directed at pathogens that have high rates of AMR across the R&D continuum (from early to advanced development).** Incentives could be provided in the form of pull incentives. (*See also Economic Issue Statement 2.*) Opportunities should be evaluated to expand federal support of grants for advanced development funding through BARDA and DoD for promising vaccines focused on preventing AMR infections.

1.3 Regulatory

Issue Statement 1: The lack of clarity about regulatory pathways for vaccines focused on AMR reduces the willingness of sponsors to produce vaccines.

The regulatory process for large, population-focused vaccines (e.g., influenza and pediatric vaccines) is well understood. Whether via well-accepted serologic endpoints, comparison with other approved vaccines, or efficacy studies, developers have a clear understanding of how these vaccines should move through the regulatory process. Vaccines intended to prevent infections from bacterial pathogens that have high rates of AMR may face a much more challenging path to approval and use if they target specific, smaller, at-risk populations; relatively uncommon pathogens; or specific pathogens that may manifest disease in multiple different syndromes (e.g., bacteremia, pneumonia, urinary tract infections, and osteomyelitis). Vaccine developers need more information about how best to develop such vaccines (types and sizes of clinical trials, acceptable end-points, etc.) and what mechanisms or pathways are available so they can frame their plans for successful regulatory submission.

The WG recommends the following:

- **Early interaction between sponsors and FDA and workshops, hosted by FDA’s Center for Biologics Evaluation and Research (CBER), explaining pathways and best practices.** While the FDA regularly interacts with vaccine sponsors, there is clear value in the agency developing a focused effort on facilitating and communicating the regulatory strategy associated with vaccines that target AMR reduction.

Issue Statement 2: The potential market for a new vaccine (as opposed to other AMR products) is uncertain, because vaccine uptake is heavily influenced by recommendations of the Advisory Committee on Immunization Practices (ACIP) and funding for vaccination.

Following approval of a vaccine by FDA, the ACIP reviews the vaccine for potential inclusion in pediatric, adult, and travel immunization schedules and for federal support for pediatric vaccines under the Vaccines for Children program. While the ACIP takes into account the efficacy and safety of vaccines, they have additional considerations, beyond those of FDA, regarding current epidemiology, programmatic and implementation issues, and cost. The lack of a comparable “Vaccines for Adults” public health access program limits the widespread adoption of vaccines that target adults, and the ultimate uptake of vaccines depends on financing. The approval of a license by FDA represents the first step in vaccine adoption; however, FDA regulatory approval of a vaccine does not necessarily equate to a

favorable use indication by the ACIP. As a federal advisory committee, the ACIP's recommendations weigh heavily on the final use recommendations issued by CDC.

To make the ACIP recommendation process more predictable, manufacturers engage with ACIP years ahead of FDA approval to discuss development programs with ACIP Work Groups. Manufacturers present these data to the ACIP prior to FDA approval, and the corresponding ACIP Work Group assesses the vaccine using a Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Following FDA approval of a vaccine, the ACIP Work Group for the newly approved vaccine presents a final review of the vaccine, and the ACIP votes on the Work Group recommendation. This vote typically takes place at the first or second meeting of the ACIP after the vaccine is FDA-approved. Following a positive ACIP recommendation, the CDC then reviews the recommendation and, if approved, publishes the recommendation in the *Morbidity and Mortality Weekly Report* (MMWR) before it becomes final, a process that can take several months.

In the current process, there can be significant variability in the way ACIP Work Groups handle their assessments and the associated time delays. While it would be inappropriate for FDA, the ACIP, or any other entity involved in a regulatory process to preordain an approval before thorough review, the time delay and uncertainty associated with the ACIP review process remains an issue for vaccine developers. A more consultative, uniform, and transparent process with CDC, as the responsible federal agency, analogous to the regular and routine consultations that occur with FDA, would give vaccine developers an improved understanding of how their vaccines will be reviewed by the relevant ACIP Work Groups and the types of data that will be important for this review.

The WG recommends the following:

- **Early communication between the manufacturer, FDA, and CDC to present and discuss a target product profile with particular reference to impact on AMR pathogens.** Development of a target product profile should be considered to reduce postlicensure uncertainty about the commercial potential of vaccines, which should include consideration of the public health AMR reduction benefits. CDC should consider the development of a process more similar to that which already occurs when vaccine developers consult with FDA on scientific issues surrounding vaccine development from a program implementation standpoint. This process, while not ensuring a particular use indication, can assist sponsors in shaping their development plans and resultant data to optimize the likelihood of a favorable ACIP/CDC use recommendation following FDA approval.

1.4 Behavioral

Issue Statement 1: Implementation strategies for optimal vaccine acceptance and utilization are inadequate.

Current evidence about the benefits of vaccines is underutilized. Many practitioners who do not deliver immunizations as frequently as pediatricians and other primary care providers do not consider immunization as part of their routine delivery of health care. Additionally, the general population does not fully appreciate the value of vaccines in prevention of disease, especially adult vaccines. An evidence-based comprehensive strategy that targets, primarily through education, health care providers and the general public for vaccination of people of all ages is needed.

The WG recommends the following:

- **Programs and interventions based on behavioral insights that aim to increase vaccine uptake.** Implementation research should be conducted to identify approaches to maximize vaccine use at an institutional level as part of AMR stewardship programs. Evidence-based policies and practices should be implemented to improve vaccine uptake, such as those found in the CDC’s *Guide to Community Preventive Services*.¹³
- **Continued, broadened economic incentives to influence behavior and increase uptake, such as reimbursement to ensure “first-dollar coverage”—that is, insurance coverage of vaccines without copayments or coinsurance costs for all ages, not just children.**

Issue Statement 2: Providers lack knowledge about the role of vaccines in preventing AMR.

While the use of vaccines in pediatrics is well established, providers are less clear about how currently available bacterial and viral vaccines can reduce the incidence of syndromes that lead to the inappropriate use of antibiotics, especially among adults. For example, effective use of influenza, varicella, and pneumococcal vaccines in adults can significantly reduce antibiotic use, yet health care providers who treat adults often do not consider this aspect of preventive medicine.

The WG recommends the following:

- **Focused governmental vaccine-centric educational policies and approaches, including vaccination as a means of achieving antibiotic stewardship, with involvement of health care facilities and health-related educational institutions (e.g., medical schools and academic health centers).**

2. Incentives for Diagnostics for Human Use

Diagnostics inform appropriate antibiotic prescribing and can reduce hospital lengths of stay, prevent hospital admissions, reduce antibiotic use, and benefit society by curtailing AMR. However, there are important clinical needs in inpatient and outpatient settings for which adequate diagnostic tests do not exist or use of existing diagnostics is limited. The cost of development, lack of clinical implementation of approved tests, inadequate reimbursement, and an expensive and complex regulatory process pose barriers to development. Use of diagnostic tests is hampered by the unavailability of tests that are practical in typical office or clinic settings (e.g., tests that provide results in 10–15 minutes) and by providers’ limited knowledge of available tests, how best to use them, and how to interpret the results. Furthermore, few outcomes studies have targeted barriers to use that could influence behavior change.

Several types of diagnostic tests impact the diagnosis and management of bacterial infections and implementation of antibiotic stewardship programs. This report addresses the following: i) antimicrobial susceptibility test (AST) devices for new antibiotics, ii) rapid tests that distinguish between bacterial and viral infections, and iii) tests that can quickly identify bacteria and allow for rapid susceptibility testing. Each of these tests is used in different clinical settings.

¹³ CDC, Community Preventive Services Task Force. *The Community Guide*, <https://www.thecommunityguide.org/topic/vaccination> (accessed August 14, 2017).

2.1 Economic

Issue Statement 1: Following approval of new antibiotics, corresponding ASTs are not immediately available to ensure proper use of the antibiotic.

As the number of infections from multidrug-resistant bacteria increases, clinicians are relying on new antibiotics that can target these bacteria to provide lifesaving treatment. Before prescribing the antibiotic, clinicians need results from susceptibility testing, but these tests are often not made available at the time the antibiotic is approved by FDA. Several factors cause a delay between the approval of a new antibiotic and the availability of a concomitant AST device. Some of the most important include delays in pharmaceutical companies engaging commercial test manufacturers, delays from commercial test manufacturers because they have test development queues, and uncertainty in clinical trial design for a commercial AST device because key pieces of information for designing a clinical trial, treatment indications by bacteria and breakpoints, are not finalized until the drug is approved.

The lack of an AST for a new antibiotic is a major impediment to use of that drug. First, neither laboratorians nor clinicians are comfortable recommending an antibiotic without some direct data of drug susceptibility by the organism, so the antibiotic is not prescribed in situations where it may be useful. Although FDA has issued draft guidance with suggestions to improve the time for AST device approval, under the current regulatory system, it may still take 2–3 years for automated updated AST devices to become available for use in clinical laboratories. Thus, use of the drug is limited because drug susceptibility cannot be confirmed. Additionally, to mitigate the impact on patient care, CDC is working with public health laboratories to implement reference susceptibility testing for new antibiotics to fill the gap between the availability of the antibiotic and the availability of a commercial test. However, the availability of a commercially available *rapid* AST, such as a gradient diffusion strip minimum inhibitory concentration (MIC) test or an antibiotic disk, when the antibiotic is approved would greatly improve the ability of laboratories to provide critical information.

The WG recommends the following:

- **Funding for the development of new antibiotics should always include the development of a concomitant *rapid* AST device.** Ideally, there would be financial support for a device manufacturing company to always provide a simple AST device, such as a disk, whenever a new antibiotic comes to market. This support does not necessarily apply to more complex automated systems. A portion of any funds provided to incentivize antibiotic development should be dedicated to development and commercialization of an AST device when the new drug is approved. The incentive would cover the cost of development and compensate for the small number of tests likely to be sold. Antibiotic developers should be encouraged to share drug formulation with diagnostics companies as early in drug development as possible to ensure that the AST device is commercially available when the antibiotic is approved. This initiative could be funded by the same mechanism(s) used for incentivizing the development of therapeutics. Sponsors should be allowed to submit their diagnostics to FDA before the drug is approved.

Issue Statement 2: Because there is no method to determine the value of a diagnostic test, reimbursement is not aligned with the value of diagnostic tests.

The level of reimbursement for a diagnostic test is an important driver of development and utilization. When determining whether to develop a new diagnostic, inadequate reimbursement to the clinical laboratory is a major disincentive, because the test may not be implemented. A laboratory's inability to recoup the cost of the test acts as a substantial disincentive to provide it for clinicians. Currently,

reimbursement for many diagnostic tests is not aligned with the value of the test. While a diagnostic test may add expense to the laboratory, it could save money for the overall health system and have a broad impact on AMR.

One example of misalignment is testing patients for carbapenem-resistant Enterobacteriaceae (CRE) colonization of the gastrointestinal tract, which is recommended by CDC as a primary intervention to prevent the spread of CRE in health care settings. When patients test positive for CRE colonization, enhanced infection control measures are implemented to reduce the risk of transmission to other patients. Because the purpose of this test is infection prevention rather than diagnosis of a patient-specific infection, the laboratory is not reimbursed. As a result, uptake of this critical testing for CRE control has been poor. Currently there is no easy method for health systems or payers to assess the value of any given test. Supplementing reimbursement for tests that detect, quantify, or characterize pathogens of public health importance could drive test development and implementation.

The WG recommends the following:

- **A “reimbursement-plus” system for tests of key public health importance (e.g., CRE colonization testing) designed with input from CMS and other public health agencies.** The reimbursement would include the cost of the diagnostic plus an additional payment to incentivize the use of the more efficacious diagnostic. This approach would consider other costs in addition to testing. For example, a nucleic acid amplification test (NAAT) costs more than an immunoassay. Both tests are reimbursed at rates close to the cost of the test (\$48 per test for NAAT and \$16 per test for immunoassays). Providers tend to choose the less expensive test because it lends itself to lower initial out-of-pocket costs and thus a lower overhead. Offering additional payment through reimbursement-plus would promote the use of NAAT, which is a more sensitive test than immunoassays. As a result, fewer patients would be prescribed antibiotics. Furthermore, this system should also reimburse for tests for infection prevention, similarly to diagnostics for patient-specific infections, because of the public health importance. This approach would promote the value of prevention.

Issue Statement 3: There is a lack of clinical and economic outcome studies showing that any diagnostic test could prevent the emergence of antibiotic-resistant bacteria and would be cost-effective.

Studies designed to evaluate clinical outcomes assess parameters such as decreased morbidity or mortality, reduced rates of infection, or complications for the study population. Cost-effectiveness studies are designed to reveal cost savings to the health care system (e.g., through reduced lengths of stay, lower rates of readmissions, or lower overall costs of care). The literature on diagnostics includes few outcomes studies, which hampers the adoption of tests. The lack of studies is particularly problematic for tests that are not currently available, such as rapid tests in the outpatient setting to distinguish bacterial from viral processes or those that rapidly identify pathogens using molecular techniques. Many of these rapid tests do not replace current diagnostics but do add costs to the laboratory. Without data to establish either clinical utility or cost-effectiveness, these rapid diagnostic tests are less likely to be implemented in clinical care.

The WG recommends the following:

- **Increase funding of diagnostics outcomes studies (e.g., from the Agency for Healthcare Research and Quality [AHRQ], CDC, the Patient-Centered Outcomes Research Institute [PCORI], NIH, and DoD), including those assessing patient outcomes, lengths of stay,**

changes in antibiotic use, rates of antibiotic use for certain patient populations, and costs of care.

Issue Statement 4: The high cost of development of diagnostics is a disincentive for diagnostics companies.

The high costs associated with the development of diagnostic tests, coupled with the potential for limited uptake, are substantial economic barriers for companies considering investing in new tests. Development is costly, as new platforms can cost anywhere from \$20 million to \$100 million, and new tests on existing platforms can range from \$10 million to \$20 million. Diagnostic development is driven by clinical needs, public health needs, and ROI. From the perspective of diagnostics companies, the primary cost drivers are prospective clinical trials, acquisition costs of rare archived specimens, and analytical studies. Current technologies are not meeting diagnostic needs. Costs are increasing at a rapid pace because of the need for better technologies, new platforms, and complex clinical outcomes studies.

The WG recommends the following:

- **Tax credit for a portion of the qualified clinical testing expense, potentially modeled after the Orphan Drug Tax Credit.**¹⁴ Qualification for the tax credit could require that the clinical testing be related to rapid infectious diseases testing and address the key unmet needs: i) a rapid point-of-care test that can be used in the outpatient setting to distinguish viral from bacterial infections or ii) tests that can rapidly identify or quantify pathogens or provide rapid susceptibility results in less than 4 hours. (*See also R&D Issue Statements 1 and 3.*) The credit should be designed in a manner that includes benefits for small, prerevenue companies.

2.2 Research and Development

Issue Statement 1: Rapid point-of-care tests are needed to distinguish between bacterial and viral infections in the outpatient setting.

A large portion of the inappropriate prescription of antibiotics occurs in the outpatient setting among patients with upper respiratory infections caused by viral pathogens. While there are point-of-care molecular and antigen tests available for detecting a few viral pathogens, most notably influenza, there are no rapid, easy-to-use, affordable, licensed diagnostic tests that can distinguish between bacterial and viral infections. Such tests also could be designed to detect host response to infection rather than pathogen DNA or antigen. Given the pressure on primary care physicians to see patients quickly in the outpatient setting, a successful diagnostic test would need to be applicable at the point of care, be very simple to use, and provide results in 10–15 minutes or less. Such a test could influence the clinician’s prescribing decisions and serve as an important tool to reduce the use of antibiotics.

Issue Statement 2: There is a need for better biomarker tests to aid clinicians in making decisions regarding when to initiate and discontinue antibiotics in the inpatient setting.

One of the challenges that clinicians face when making the decision to initiate antibiotics is distinguishing patients with bacterial infection from those with syndromes caused by a noninfectious etiology, such as heart failure or exacerbations of chronic obstructive pulmonary disease. There are no standardized parameters for appropriate or safe discontinuation of a course of antibiotics. The availability of a test that

¹⁴ *Orphan Drug Act*, Public Law 97–414, U.S. Statutes at Large 96 (1983): 2049.

measures host response would facilitate a move away from regimented, prescribed courses of antibiotics to an individualized approach to treatment, possibly reducing the duration of antibiotic therapy. An effective test could safely shorten the average duration of treatment and lessen antibiotic pressure of selective resistance.

Issue Statement 3: Tests are needed that rapidly identify or quantify pathogens directly from the clinical specimen and provide rapid susceptibility results.

Other key unmet needs are the ability to identify bacteria directly from a clinical sample rapidly (within 1–2 hours) and also provide rapid susceptibility results (within 4–6 hours). There has been progress in the development of methods that rapidly identify bacteria and provide limited susceptibility results from a positive blood culture. Although the data are not always complete, depending on the pathogen, the test results can serve as an important aid to antibiotic stewardship programs. The ability to detect, identify, or provide susceptibility results directly from a clinical specimen would be transformative in managing patients with bacterial infections, informing decisions regarding initiating therapy or narrowing antibiotic coverage much faster than current methods.

The WG recommends the following:

- **Sustained investment in funding mechanisms (e.g., grants) for developing new, cost-effective diagnostic tests and updating existing diagnostic tests (through Small Business Innovation Research (SBIR) and Small Business Technology Transfer grants, among others).**
- **Expanded funding for clinical trials networks (e.g., NIH-supported Antibacterial Resistance Leadership Group [ARLG]) and applied innovation networks (e.g., CDC-supported Prevention Epicenters) and assurance that these networks work through a common institutional review board (IRB).** Funding of these networks could be used for various types of studies, including tests for new diagnostics, outcomes studies, cost-effectiveness studies, and comparison studies.

Issue Statement 4: Collaboration between diagnostics companies and other stakeholders is limited and inconsistent.

Development of a rapid diagnostic test requires substantial investment for companies. There is variability in how and when companies reach out to diagnostics and clinical experts for input. Increasing the interactions between diagnostics companies, clinicians, and clinical laboratorians prior to or early in the test design phase could help ensure optimal test development to meet clinical needs and increase the likelihood of adoption of the test into clinical practice.

The WG recommends the following:

- **Federal government agencies (e.g., HHS, FDA, CDC, NIH, DoD, USDA) should come together to create a list of the most critically needed diagnostics for combating AMR.** The list could be used to prioritize funding and tax credits.

2.3 Regulatory

Issue Statement 1: The regulatory approval clearance process for modifying and improving existing diagnostic tests is complex and expensive.

A major barrier to improving a test, once it is FDA-cleared, is the regulatory requirement for altering an assay. Improvements in tests include modifying a primer pair, adding a specimen type, adding a pathogen to a multiplex panel, or updating an AST panel to include a new antibiotic. Conducting the clinical studies and other studies needed for regulatory approval is a substantial burden for companies, and it is often difficult for companies to recoup this investment because the improved product will have neither a higher reimbursement rate nor be sold for a higher price. When improvements are delayed or lacking, clinical laboratories that have adopted specific instruments or platforms may be running tests with less-than-ideal performance characteristics. To assist companies in the challenges associated with the regulatory approval process, FDA has started accepting real-world evidence and postmarket data for regulatory approval of diagnostic test modifications. For example, procalcitonin uses were expanded based on postmarket data. Additionally, numerous assays have been modified when unexpected isolates emerged with different performance characteristics (e.g., hepatitis B and cytomegalovirus mutants).

The WG recommends the following:

- **Advancing FDA regulatory efforts for improvements or updates of existing tests that utilize postmarketing study results and real-world evidence to promote development of improved tests.** FDA should continue to encourage the use of postmarketing studies and real-world evidence when such an approach can reduce time to market for improved diagnostic assays. Sponsors should consider and propose models for the use of real-world evidence and postmarketing studies to support regulatory actions (e.g., collecting less-prevalent organisms postmarketing or genotypic assays where confirmatory susceptibility testing is performed). FDA should sponsor a workshop with a diverse group of stakeholders to discuss how to use postmarketing studies and real-world evidence to support regulatory action.

Issue Statement 2: The current regulatory process for new diagnostics is time-consuming and costly, posing a disincentive for developers.

Regulatory approval of new diagnostic tests requires analytical studies and prospective clinical trials. Challenges include acquiring appropriate numbers of rare specimens and generating data for all antibiotic/bacteria combinations. The length of the regulatory review and approval process is problematic for developers in a rapidly evolving clinical and market environment. Also, identifying clinical trial sites and working through the offices of research affairs and IRBs for each institution further lengthens the process. Typically, three clinical trial sites are required, but for tests addressing rare pathogens, such as multidrug-resistant bacteria, more sites may be needed to identify an adequate number of cases for the clinical study. It is extremely cumbersome for diagnostics companies to identify sites and train staff accordingly (i.e., in the use of gold-standard methods that may no longer be used routinely in clinical laboratories, such as viral culture). All of these issues add to the expense and time required to conduct clinical trials.

The WG recommends the following:

- **Additional or enhanced clinical trials networks that function with a common IRB to reduce the regulatory burden of test approval.**

- **Modification of requirements to simplify process for obtaining Clinical Laboratory Improvement Amendments (CLIA) waivers.**
- **Utilization of postmarketing study results and real-world evidence to facilitate the approval process of new diagnostics.**
- **Complementary structuring of the FDA-CDC Antimicrobial Resistance Isolate Bank and the ARLG virtual repository to increase diagnostics companies' access to isolates.** CDC should work to fill any isolate gaps by accessing clinically- and microbiologically-defined isolates from a variety of sources, including the ARLG. The FDA-CDC bank is linked to the ARLG virtual repository. The ARLG virtual repository could focus on collecting primary clinical specimens (e.g., blood, urine, stool, and respiratory specimens) that would be available to diagnostics companies for test development.

Issue Statement 3: Hospitals are not required to update their microbiology laboratories with newer technologies.

Clinical studies demonstrate that newer tests, coupled with an active stewardship program, can be very effective in reducing the inappropriate use of antibiotics, reducing treatment of blood culture contaminants, and shortening the duration of antibiotic coverage. For example, existing tests that distinguish methicillin-susceptible from methicillin-resistant *S. aureus* and coagulase-negative staphylococci provide therapeutic information within 1–2 hours after the blood culture becomes positive and can inform antibiotic prescribing. However, not all laboratories adopt these new and improved tests, because there is no incentive or requirement that they implement new technologies that improve outcomes. Similarly, while updated breakpoints for antibiotics are published annually by the Clinical and Laboratory Standards Institute (CLSI), there is no mechanism to ensure that these changes are implemented in clinical laboratories before the next inspection (which occurs every 2 years). Finally, laboratories are not required to discontinue use of tests with inadequate performance characteristics (e.g., low sensitivity, poor specificity) or technology that has become obsolete. As a result, clinicians may receive misleading information from the laboratory.

The WG recommends the following:

- **CLIA requirements to update microbiology laboratories' technology as part of the accreditation process.** For example, require laboratories to adopt updated breakpoints and newer technologies (e.g., matrix-assisted laser desorption/ionization-time of flight [MALDI-TOF] and multiplex polymerase chain reaction [PCR]) once available as a condition of approval.

2.4 Behavioral

Issue Statement 1: Clinicians do not always use diagnostic tests, believe the results, and act on them.

Limited use of diagnostics, especially in the outpatient setting, stems from the lack of a licensed test that can rapidly distinguish bacterial from viral infection, but other behavioral issues are involved. To increase the use of rapid diagnostics, it is essential to better understand the barriers that prevent clinicians from using them. The problem is circular: poor uptake of tests in clinical practice is a substantial barrier to test development and a major disincentive for diagnostics companies. There is very limited information describing why clinicians do not use diagnostic testing. In addition, clinicians lack knowledge regarding what tests to order, when to order them, and how to interpret results. Educational programs could address

the gaps and allow clinicians to better use diagnostic tests in their clinical practices. The availability of outcomes data describing the value of diagnostic tests could also influence clinician behavior.

The WG recommends the following:

- **Evidence-based research, supported by public and private resources, to facilitate a better understanding of the behavior that affects decisions about using rapid diagnostics, with a goal of identifying drivers that prevent adoption.** Specific areas of focus could include assessment of outpatient upper respiratory infections and rapid identification of bacteria from a positive blood culture.
- **Inclusion of experts in clinical use of diagnostics who can provide information regarding appropriate use of relevant rapid tests on clinical guidelines committees that address prevention, diagnosis, and treatment of infectious diseases.**
- **Clinician education on the use and interpretation of diagnostic tests.** Working through accreditation agencies, education programs should be added to the medical school curriculum and residency training programs and can be linked to stewardship education. For currently practicing clinicians, continuing education could be conducted through professional organizations, diagnostics companies, and public health campaigns such as those conducted by CDC. Topics could include best practices for ASTs and use of the rapid streptococcus test before prescribing antibiotics. Educational programs for the public should address AMR and the value of diagnostics—for example, through CDC’s Get Smart About Antibiotics program.
- **Development of tools and mechanisms that improve clinicians’ abilities to make decisions in the ambulatory setting (e.g., linking antibiotic prescriptions, accompanied by laboratory results, to pharmacy dispensing of antibiotics and antivirals through an electronic medical record).**

3. Incentives for Therapeutics for Human Use

Although USG efforts to date have been supportive, incentivizing development of innovative therapeutics, specifically antibiotics, to address antibiotic-resistant infections will require transformative measures to create a vibrant, diverse, and robust product pipeline linked to a sustainable global marketplace. Driving these changes is the insight that antibiotics are precious resources with societal benefits that are much larger than benefits obtained from treating a given infection. Much as the residents of an apartment building benefit when a fire extinguisher prevents a kitchen fire from becoming a building fire, promptly treating an infection with an effective antibiotic benefits both the treated patient and all the individuals who now will never need to take the antibiotic because the infection was halted at the source. Indeed, the existence and availability of a diverse array of antibiotics acts as insurance against future epidemics. Therefore, this availability should be considered as a metric when the USG, other governments, payers, and other potential investors consider the value of these drugs.

A fundamental conundrum arises from the need for antibiotics to be available but used only as absolutely required. Even appropriate and effective use entails a risk of subsequent resistance as bacteria evolve. As a result, diverse, long-term innovation is needed, as is recognition of the societal value of having an antibiotic available in the pharmacy even if it is not used on any given day in any given patient.

A free market for antibiotics is likely to fail for two reasons. First, individual patients, physicians, and pharmaceutical companies fail to consider that the use of any antibiotic gradually reduces its effectiveness

for others. Second, caps on reimbursement have introduced inefficiencies in how antibiotics are priced and could lead to suboptimal marketing strategies that emphasize sales volume and a rapid depletion of antibiotic effectiveness. Key stakeholders, including the USG and drug manufacturers, have different perspectives on the approaches needed to overcome the way these market failures have led to stagnation in antibiotic R&D. Piloting a combination of solutions is likely necessary.

3.1 Economic

Issue Statement 1: The ROI for developing new antibiotics is unpredictable because of antibiotic resistance and related restrictions on use of new agents.

The stream of revenues for new antibiotics is unpredictable because of rising antibiotic resistance (i.e., sales taper off as resistance develops). The overall cost of drug development is increasing over time. The easier-to-find antibiotics have already been developed; new types of antibiotics are increasingly more difficult to find and design. The willingness of health payers (private and public) to pay for antibiotics is anchored to the cost of older, generic antibiotics like penicillin, which often are sold for pennies a pill, and is not consistent with the high costs of new antibiotic development. Because of these factors, manufacturers are more likely to invest in other types of products (e.g., statins or diabetes drugs), for which ROI directly correlates with the volume of product sold.

The WG recommends the following:

- **A combination of general and targeted incentives to introduce a more predictable and sufficient ROI for antibiotic manufacturers, including push incentives (e.g., grants, transferable tax credits, support for clinical trial networks and initiation of common clinical trials, and government-funded milestone payments during development) and pull incentives (e.g., market entry rewards [MERs], transferable exclusivity vouchers, and value-based reimbursement through the development of alternative payment models).**
- **Expansion of targeted push incentives across all phases of discovery and development.**
- **Adoption of some form of a delinkage model as a pull incentive.** Delinkage is a proposed model to incentivize the development of new drug products in which profitability is separated from sales volume. The pull incentives most likely to be effective in the U.S. market are all variations on the delinkage models proposed by DRIVE-AB and the Duke-Margolis Center. A core feature of this model is an agreed-upon payment for the delivery of a given antibiotic to the marketplace—or an MER—rather than a payment based on the use of the product. The value or price of the MER is benchmarked (indexed) to reflect the level of public health need that would be addressed by the new antibiotic product. Different approaches for setting the value of the MER should be debated—recent work has suggested that total values may need to be \$1 billion to \$2 billion or more. Fixed value based on desired characteristics of the drug will be the easiest to measure. Approaches based on assessing utility in the clinic are desirable but will be confounded by the limited use that is both expected and desirable with these products. Receipt of the MER should be tied to restrictions on sales and marketing through use of a delinkage model. Plausible options for paying for pull incentives include establishment of an antibiotic incentive fund (AIF) supported by an antibiotic usage fee, by auctioning transferable exclusivity vouchers, or by allowing registration of a new antibiotic to earn a transferable exclusivity voucher. Government appropriations also could be considered, but experience shows that these are unpredictable and likely not sustainable. Under a delinkage model, the drug developer retains all intellectual property (IP) and has responsibility for approval, manufacturing, and sales of the

antimicrobial. However, by accepting MERs as payments from the AIF, the company would have to agree to forgo profits based on volume of sales and to forgo active marketing of the product. The major advantage of this approach is that government could prioritize health products for unmet medical need. Disadvantages include the political challenge of committing to funding for new products, defining the value benchmarks, and allocating the cost of the delinkage payments to the consumer market.

- **For pull incentives, development by CMS and the Treasury Department of value metrics for antibiotics and diagnostics, the required size of delinked MER rewards, and options for plausible business models for antibiotics, including delinkage, in consultation with FDA and CDC, and through collaboration with public health experts and the international community.**

3.2 Research and Development

Issue Statement 1: Finding molecules that kill bacteria without also harming the patient is scientifically challenging.

Nearly all antibiotics currently available for patients are based on discoveries initially made over 30 years ago. New classes of antibiotics offer the promise of being active with only limited amounts of preexisting resistance. Efforts to discover new class compounds have included searches for novel natural products (antibiotics arising naturally in nature) and novel manmade molecules. Although it is common to find molecules that can kill bacteria, the discovered molecules also have consistently had properties that made them unsuitable as drugs. The most common flaw is that the molecule is found to be toxic. Other problems (e.g., the molecule does not distribute properly in the body) are also seen. Therefore, more novel discoveries are needed to kill the bacteria without harming the patient.

The WG recommends the following:

- **Strengthened funding for existing mechanisms that support innovation and R&D, including:**
 - CARB-X to stimulate the early-stage development of promising new antibacterial therapies;
 - NIH/National Institute of Allergy and Infectious Diseases (NIAID) preclinical and clinical support services to fill gaps in product development pathways;
 - NIH funding opportunities (grants and contracts) for research aimed at advancing the discovery of urgently needed new types of antibiotics;
 - ARLG; and
 - BARDA's Broad Spectrum Antimicrobials program to advance the development of novel antibacterial and antiviral drugs to address the threat of antibiotic resistance and establish innovative public-private partnerships that support advanced R&D of a portfolio of antibiotic candidates.

Issue Statement 2: Showing the utility of a new antibiotic against resistant bacteria paradoxically requires that resistant infections occur with sufficient frequency to enable clinical study.

Infections caused by rare or resistant bacteria are currently infrequent, which is desirable from a public health perspective. However, the low frequency of these infections makes studying new antibiotics challenging in the clinical setting. Yet, new types of resistant bacteria can emerge with remarkable speed. Therefore, development of new antibiotics is needed in advance of widespread resistance.

The WG recommends the following:

- **Continued development and refinement of FDA guidance documents, with particular and urgent emphasis on expanding the guidance on narrow-spectrum agents that address unmet medical need.** (*See also Regulatory Issue Statements 1 and 2.*)
- **Clinical trials networks, based on common master protocols and facilitated by BARDA and NIH, to accelerate Phase II and Phase III programs for agents that have adequate spectrum to permit study in the common infections for which standard trial designs exist.** A clinical trials network that operationalizes common master protocols at a level of quality that matches the pharmaceutical industry would bring greater efficiency to the antibiotic R&D enterprise, save time and money, and facilitate an agile response to future needs. Master trials that apply common clinical test protocols to multiple groups of patients while sharing a common control group have been successful in advancing cancer drug R&D. The quality of such a risk-sharing network should be at a level such that pharmaceutical companies would welcome the opportunity to perform their core development program using the common protocols that are housed within the clinical trial network. Such a clinical trials network would allow pharmaceutical companies to utilize shared expertise and infrastructure to study antibacterial drugs. These networks should focus initially on gram-negative indications (complicated urinary tract infection, complicated intra-abdominal infection, and nosocomial pneumonia). They could serve to build clinical trials capacity, facilitate study of less common pathogens, and facilitate study of diagnostic devices.

3.3 Regulatory

Issue Statement 1: It is difficult for manufacturers to develop clear and specific data for any new drug on clinical efficacy in infections caused by highly resistant bacteria.

Issue Statement 2: It is difficult to enroll the number of patients needed to show efficacy of a narrow-spectrum antibiotic because of the low rate of infections caused by specific pathogens.

Sponsors of narrow-spectrum agents face an additional struggle in that the low rate of occurrence of infections caused by specific target pathogens (whether antibiotic-resistant or antibiotic-susceptible) makes it hard to enroll the number of patients required to provide the level of substantial evidence expected by the regulatory and payer communities. The establishment of clinical trials networks based on common master protocols could be helpful in identifying and enrolling these patients. (*See also R&D Issue Statement 2.*)

The WG recommends the following:

- **Establishment of clear expectations by FDA through regular stakeholder engagement as guidance is developed.** Guidance should outline the progression to approval of drugs for unmet medical need using strategies that can be feasibly implemented on a routine basis using the available small-size patient populations that are relevant for the new agent at hand. In particular, FDA should use the limited population antibacterial drug (LPAD) pathway as an impetus to allow antibiotics for resistant infections to come to market through streamlined clinical trials and help ensure these products are not used inappropriately in more general populations.

- **Development by CMS, the Treasury Department, and other USG agencies of approaches to assess antibiotic value using limited amounts of data.**

3.4 Behavioral

Issue Statement: Stewardship activities appropriately limit the use of current and new antibiotics; therefore, novel antibiotics have a low financial ROI from the perspective of the developer.

Models of care and alternative payment models are evolving. Exhaustive analyses have shown that the free market does not function well for antibiotics because of the entirely appropriate need to minimize the use of new agents so that their activity is preserved. In this regard, fire extinguishers and antibiotics have a great deal in common—we want both available at all times but we do not want to ever have to use them. The model of paying for availability is well established for fire prevention and firefighting services, but this model has never been developed for antibiotics. Instead, the current pay-per-use model for antibiotics is tantamount to only paying for a fire extinguisher when one is actually used against a fire. It is apparent that this model cannot sustainably pull new antibiotics forward and that new business models must be developed. The need for these models is discussed above. Incorporating features that ensure good stewardship should be straightforward and must be kept in mind.

The WG recommends the following:

- **Continued efforts by CMS and the Treasury Department to ensure that solutions to the problem of incentives incorporate and support stewardship.** Specifically, delinked business models that are independent of usage should be developed, in consultation with FDA and CDC.

SECTION II. ANIMAL HEALTH

Antibiotics have been an important therapeutic tool for bacterial infections in livestock, poultry, and companion animals for over 60 years. The contribution that the administration of antibiotics to food animals makes to the overall problem of antibiotic resistance in foodborne bacteria and in medical settings remains to be quantified. It is widely acknowledged that selective pressures from antibiotic use in any setting will likely increase the prevalence of antibiotic-resistant bacteria; therefore, opportunities to replace, refine, or reduce antibiotic use should be examined.

Veterinary medicine is more diverse than human medicine because of the wide variety of animal species and their associated pathogens and the environments in which they are maintained. Companion animal medicine is most similar to human medicine, as care is predominantly focused on individual patients. While the WGs acknowledge the role that antibiotic use in companion animals plays in AMR, the challenges faced by developers of vaccines, diagnostics, and therapeutics/anti-infectives differ between companion animals and food animal production. Therefore, to appropriately limit the scope of the WG's task, companion animals were excluded from the WG assessments.

Food animal veterinarians' responsibilities are to protect animal health and also to protect public health by supporting the integrity of the food supply. Although individual animal care remains important, the main focus of food animal medicine is at the population level (i.e., groups of animals in pens, barns, or ponds). When considering an antibiotic treatment, animal producers and veterinarians have to consider not only effects on the pathogen underlying the disease directly affecting the animal, but also potential off-target side effects. The impact on other bacteria that may be present, including foodborne pathogens such as *Salmonella* or *Campylobacter*, and the downstream effects of treatment choices on the consumer and the environment also are critical considerations.

Initiatives to ensure the appropriate use of medically important antibiotics in food animal agriculture, such as FDA's Center for Veterinary Medicine (CVM) Guidance for Industry,^{15,16} in addition to a growing consumer preference for food raised without antibiotics, contribute to the current trend of using fewer antibiotics in animal agriculture. However, because animal disease outbreaks will continue to occur, antibiotics will continue to play an important role in maintaining animal health and well-being on most farms.

Another unique aspect of animal health is the cost of treatment and prevention. In human health care, insurance companies and government programs offset some costs to the recipient of health care. In animal health, the food animal industry, specifically the producers, absorbs the total cost of medications or interventions. The sales revenue of food animals or their products (e.g., milk or eggs) at market is the most realistic way to assess the ROI for the intervention used. The ROI can be measured by performance

¹⁵ FDA Guidance for Industry #209: *Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals* (FDA, 2012), <https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf>

¹⁶ FDA Guidance for Industry #213. *New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drink Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209* (FDA, 2013), <https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf>

parameters such as feed consumption/efficiency, daily weight gain, time to reach market weight, and decreased animal loss due to death.

Under a One Health approach, animal production practices should not only benefit animal health and welfare but food safety and public health as well. Conversely, research and clinical practices developed for human health may contribute to improving animal health. When viewing the problem of AMR from a One Health perspective, a consistent concern is the disproportionately lower allocation of funding for research in animal health compared with human health. Antibiotic-resistant bacteria can be shared among species, including humans, which clearly demonstrates the need for a cooperative approach between the animal and human health sectors. Yet, there are far fewer resources allocated for AMR research and interventions in animal health than are needed. The WGs see potential for agencies that deal with human health concerns of zoonotic bacteria to consider funding projects related to animal health as another means to reduce human disease, and specifically, disease caused by AMR bacteria of animal origin.

Given the need for innovation to minimize and contain antibiotic-resistant bacteria before they enter the food chain, the time is right to stimulate the development of novel approaches that will reduce the need for antibiotic use in food animals as well as make therapeutic uses more strategic and effective. The major recommendation within this section is drafting of a National Policy on Innovation for Food Animal Disease Interventions as a forerunner to the creation of an interagency Innovation Institute.

National Policy on Innovation for Food Animal Disease Interventions

The proposed U.S. National Policy on Innovation for Food Animal Disease Interventions is envisioned to serve as a charter for the Innovation Institute, laying out the vision and mission, operational aspects, and funding requirements. Furthermore, the policy would provide a general outline for the Innovation Institute's role in the development of vaccines, diagnostics, and alternatives to antibiotics and their use in food animal production. A panel of representative stakeholders from government, industry, veterinary medicine, food animal production, food retailers, universities, foundations, and other sectors would be convened to draft the Policy.

Innovation Institute

The proposed Innovation Institute would facilitate public-private partnerships by serving as a “one-stop shop” for entrepreneurial researchers, small-to-medium size enterprises, startup companies, and universities to access the resources needed to advance their technologies to initial commercialization. The proposed Innovation Institute would operationally be situated within USDA and would promote exchanges and interactions across sectors. The Institute would connect interested parties to the existing research, technology transfer, and regulatory services provided by the USG, including FDA, CVM, USDA, or other agencies (e.g., the U.S. Patent Office, the Small Business Administration, BARDA, NIH, CDC, and DoD). It would also establish connections with nongovernmental entities, such as veterinary medical organizations, animal health companies, associations (e.g., Animal Health Institute, Kansas City Animal Health Corridor, and Biotechnology Industry Organization), food animal production companies, and universities to promote exchanges and interactions across sectors.

Initial funding, staffing, and operation would come from within participating agencies. Ideally, the Innovation Institute would become a self-sustaining public-private partnership over time, with new funds generated to offset some USG funding. Revenue could come in the form of fees for users; directory listings for contract research operations or consultants; or grants from associations, companies, or other organizations.

1. Incentives for Vaccines for Animal Use

Vaccine use has been a cornerstone of disease prevention in all commodities of animal agriculture for decades. However, incentivizing new vaccine development and use is a novel concept for agriculture. Currently, USDA has research programs in place for development of new vaccines for catastrophic diseases, such as influenza and foot-and-mouth disease, as well as limited vaccine discovery research programs for the more common diseases faced during the production cycle. Private companies also actively pursue vaccine discovery research; therefore, public–private partnerships are important to advance R&D and use of veterinary vaccines. This research is market-driven. A recent report from the World Organization for Animal Health (OIE) identified a significant number of animal diseases for which antibiotics are used extensively because of the inadequate availability of suitable vaccines (e.g., vaccines that are effective and deliverable through mass vaccination) in animal production. Importantly, developers and users decide what vaccines to market or use based on economic drivers.

Vaccine use in animal agriculture could reduce the emergence and spread of AMR bacteria in two ways. First, vaccines could prevent diseases in animals so that fewer antibiotics are needed for treatment. This reduction can be accomplished through vaccines targeted to bacterial pathogens of food animals or by targeting viruses that can predispose animals to secondary bacterial infections. Second, vaccines could target zoonotic bacteria carried by healthy animals but potentially pathogenic to humans (e.g., food safety pathogens like *Campylobacter*, *Salmonella*, and enterococci). This second approach could reduce human illness caused by bacterial pathogens on contaminated food products, and, as a result, reduce the need for and the amount of antibiotics used to treat people.

Like all interventions in animal agriculture, 100 percent of the cost of the intervention is borne by the producers. Animal vaccines that target bacteria that are pathogenic to humans, but not to the animal, are not economically viable unless producers are compensated for their use of the vaccines. Thus, the challenge lies in figuring out ways to incentivize the development and use of vaccines that could decrease AMR risk to animals and humans, particularly when they incur costs without tangible benefits to producers at the production level.

1.1 Economic

Issue Statement 1: The cost of purchasing and administering vaccines can outweigh the cost of purchasing and administering antibiotics.

One well-established method for disease prevention in animal agriculture is the prophylactic use of antibiotics. Currently, a number of antibiotics are FDA-approved and labeled for preventing specific diseases in certain animal populations. These antibiotics tend to be older, so inexpensive generic versions are usually available and are effective at preventing disease. As a result, producers need incentives to use vaccines that can be more expensive and less effective than antibiotics. Incentives could be rationalized by estimating the anticipated improvement in food safety and public health in economic terms of reduced foodborne disease burden (particularly focused on bacteria identified by CDC as the biggest threats to AMR¹⁷). Similarly, use of vaccines can contribute to the health and welfare of food animals in a “raised without antibiotics” production program, making such programs more appealing for producers.

¹⁷ CDC, *Antibiotic/Antimicrobial Resistance: Biggest Threats*, https://www.cdc.gov/drugresistance/biggest_threats.html (accessed August 14, 2017).

The WG recommends the following:

- **Incentives for use of vaccines that reduce bacterial disease prevalence in farm animals to reduce the need for antibiotics.** Incentives for reducing zoonotic bacteria in farm animals that do not impact animal health are needed, possibly through a premium paid for animals at slaughter that received vaccines with the potential to reduce loads of bacteria that pose a human health concern. The USDA Agricultural Marketing Service’s Process Verified Program may offer a model for this approach.

1.2 Research and Development

Issue Statement 1: There is limited funding for basic research on the immune system in key animal species, which is fundamental to designing the next generation of vaccines, adjuvants, and administration tools.

Knowledge gaps must be addressed by basic research to successfully develop more effective and longer-lasting animal vaccines for a broader range of pathogens and diseases. Fundamental research is especially needed on the basic understanding of diverse immune systems across animal species to target vaccine development for optimal protective responses. There is also a significant gap in the availability of veterinary immunological reagents, which impedes research aimed at understanding mechanisms used by pathogens to escape the immune system or mechanisms of protective immunity. Without adequate funding for such research, researchers and developers have no choice but to pursue vaccine development using outdated approaches. Prioritization of research gaps can help focus scarce research funding on the most promising and impactful areas for reducing reliance on antibiotics to manage animal disease and innovative vaccine development. Furthermore, researchers must seek out and manage expertise in legal and financial contracts, study designs, experimental material, research animals, animal housing and care protocols, sampling protocols, data collection and documentation, information technology, statistical evaluation, and more. It takes time to find the right partners, and the process is inefficient and costly. Innovators can benefit from clear jurisdictional and directional insights from regulatory agencies for their novel vaccine candidates.

The WG recommends the following:

- **Funding from the Innovation Institute dedicated to supporting basic research of immune systems across species to optimize vaccine and adjuvant development, with shared funds across agencies, as this issue addresses AMR in both human and animals.**
- **Sufficient funding for the proposed Innovation Institute within USDA to develop new technology accelerator programs.** This recommendation complements the ongoing work of USDA, yet adequate funding for USDA has not been provided. Public–private partnerships are key to delivering needed innovation that is necessary to maintain and improve food animal health as an essential component of domestic food productivity and even international trade. Additionally, emphasis should be placed on the development of animal vaccines that prevent human disease but do not have a benefit for animal health or production. The proposed Innovation Institute would support a sustainable, coordinated approach to new research. Targeted funding to USDA or other appropriate entities might be needed if extramural research does not adequately cover identified data gaps.

Issue Statement 2: Vaccine delivery systems for mass vaccination are not optimized for specific animal pathogen production scenarios.

Routes of vaccine administration vary depending on the species, the pathogen, and the production setting. Some vaccines are administered to individual animals via injection, but a critical gap for intensive animal production systems is the lack of delivery systems for mass vaccination of millions of animals (e.g., administered at a population level by an oral, immersion, or aerosolized route). For example, it is neither feasible nor cost-effective to inject every single chicken on a farm of thousands. Additionally, not all vaccines are amenable to different routes of delivery. Research is needed to identify the most efficient and effective vaccine platforms (e.g., through addition to drinking water), particularly how to overcome challenges to mass vaccination.

The WG recommends the following:

- **Funding provided by the Innovation Institute dedicated to supporting improved vaccine delivery in animal production, with shared funds across agencies, as this issue addresses AMR in both human and animals.**

Issue Statement 3: Epidemiological data are insufficient about the use of antibiotics for infections caused by pathogens that are currently or potentially preventable through vaccination.

Epidemiological studies and models are needed to show how a vaccine could reduce AMR through reduced antibiotic use and yield ROI for health management programs. Models could demonstrate the effectiveness of a properly used vaccine, the benefit to animal health, and the ROI, which could result in a net reduction of antibiotic use. For example, if the efficacy of a vaccine is low, animals will still need antibiotics to treat the disease that was not successfully prevented. A predictive model would allow the end-user to decide how and which vaccines to use.

The WG recommends the following:

- **Increased collaboration with public–private partnerships and specific studies to estimate amount of antibiotic use that can be eliminated with vaccines, including viral disease vaccines.**

1.3 Regulatory

Issue Statement 1: Regulatory processes prevent a flexible approach and rapid approval of vaccine strain updates in vaccine development.

Vaccine manufacturers must identify emerging new strains and modify their vaccine products to counter new pathogens. Because time is of the essence to get products to market to safeguard animal health, the regulatory system must also be responsive in a timely manner. However, vaccine manufacturers face barriers to updating vaccines that could reduce vaccine uptake. For example, current USDA guidance¹⁸ indicates that strains within equine and swine influenza vaccines can only be updated after demonstrating an expectation of reasonable efficacy.

¹⁸ USDA, Animal and Plant Health Inspection Service, *Veterinary Services Memorandum 800.111* (USDA, September 19, 2007), https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_111.pdf

The WG recommends the following:

- **Process evaluation by USDA’s Center for Veterinary Biologics (CVB) to improve the speed of approval of new strains in commercial vaccines.** USDA should consider the potential to allow more rapid strain updates based on use of the current approved Outline of Production and evaluation of clinical efficacy in the field. The same process should be considered for strain updates in other inactivated bacterins and virus vaccines. Currently, CVB requires manufacturers to develop an Outline of Production that describes how a product is formulated, tested, packaged, dated, and recommended for use. By using the approved Outline of Production, a vaccine or bacterin manufactured using that same Outline with updated antigens could be reasonably expected to be pure, safe, and potent without the need for additional animal work to demonstrate efficacy.

1.4 Behavioral

Issue Statement 1: It is challenging for producers and veterinarians to integrate new vaccines and vaccination strategies into overall health management strategies while balancing productivity, animal welfare, and ROI.

Incorporating vaccines into health management programs requires an understanding of the effectiveness of a vaccine to improve ROI, animal welfare, and productivity and its role in reducing AMR. More data are needed to convince producers and veterinarians to increase their use of vaccines. In animal agriculture, vaccines are direct costs for the producers. When clear animal health or economic benefits are evident (e.g., porcine circovirus type 2), vaccine uptake may be rapid and extensive.

The WG recommends the following:

- **Education and training in assessing the effectiveness of disease prevention programs that balance productivity and welfare through improvements in veterinary and animal science curricula, continuing education, and funding for training programs that assess herd and flock health programs.**

2. Incentives for Diagnostics for Animal Use

The United States has advanced animal diagnostic infrastructure through its state and federal veterinary diagnostic laboratories. These laboratories have demonstrated the ability to rapidly develop, implement, and scale up diagnostic testing to meet industry needs. They also play a central role in control of endemic diseases, including conducting AST.

Identifying the cause of disease in food animals integrates clinical history, data analysis, clinical or postmortem examination, and laboratory diagnostic tests. In all species, a relatively small number of well-characterized diseases accounts for a large proportion of morbidity, mortality, and therapeutic interventions. These common conditions often occur at predictable points during the lifetime of food animals and may be related to management events (e.g., weaning or transport). Routine monitoring of mortality and morbidity is a core element of health management that can trigger further diagnostic efforts and initiation of therapy. Necropsy (often coupled with laboratory submissions for pathology, agent detection, and AST) is a fundamental diagnostic procedure that underpins health management in food animal populations. Within these population approaches, the costs of diagnostic testing are relatively less prohibitive than when employed for individual (e.g., companion) animals. However, laboratories are often remote, which leads to delays in diagnostic test results.

2.1 Economic

Issue Statement 1: Clinical outcome studies are needed to show that the use of diagnostic tests could prevent or quickly detect the emergence of antibiotic-resistant bacteria and is cost-effective.

Historically, much of clinical veterinary medicine—including when to use an antibiotic and which one—has been based on basic principles, acquired through education and complemented by practical experiences, often derived from empirical treatments and observations. Demonstration of efficacy is required for registration of antibiotics for labeled indications in food animals, but legal extra-label drug use (under the Animal Medicinal Drug Use Clarification Act of 1994) is common in all industries. Although treatment is moving toward more evidence-based approaches, for many indications there are few outcomes-based clinical trials, especially using the “gold-standard” approach of randomized, controlled trials. The paucity of outcomes-based animal studies limits the understanding of all aspects of antibiotic use in animals, including the impacts of administration (i.e., drug, dose, route, and duration) on an array of relevant outcomes such as clinical efficacy (animal health and well-being), the impact on antibiotic resistance at individual and population levels, and the economic implications of different therapeutic options. Information is also scarce about how diagnostic tests can be most effectively employed in food animal medicine.

The WG recommends the following:

- **Funding from the Innovation Institute for diagnostics outcomes studies, including animal health and welfare outcomes, AMR, and the impact on cost of production.** For all major food animal species, research should identify three to five of the most prevalent diseases and syndromes against which antibiotics are most commonly used. Information about preferred diagnostic strategies (both clinical and laboratory-based) and interventions (antibiotic use and others) could be acquired by methods such as systematic review or expert opinion. Randomized, clinical trials that compare different diagnostic approaches and potential interventions with respect to animal health, antibiotic resistance, and economic outcomes would enhance understanding of the animal health and potential human health risks and benefits associated with clinical decisions involving antibiotic use.

Issue Statement 2: The use of diagnostic testing can be limited by the expense incurred.

Ideally, an evidence-based approach to antibiotic prescribing would include universal diagnostic testing to confirm the specific diagnosis coupled with AST to evaluate treatment alternatives. The extent to which the cost of diagnostic testing dissuades clinicians from requesting tests varies greatly among clinical settings, as does the value of additional information that could be obtained via testing. Diagnostic costs are less prohibitive for larger enterprises than for smaller farms or when used for individual testing. Some larger enterprises have a high volume of laboratory submissions and can track AST patterns for priority pathogens over time to guide therapeutic decisions. This approach is more difficult for smaller farms, for which the cost of testing is a greater burden.

The WG recommends the following:

- **Ongoing financial support for veterinary diagnostic laboratories that perform diagnostic testing and AST for animal pathogens.** Funding should ensure adequate resources (equipment, supplies, and funds) are available to provide affordable services to individual clients but also to collect animal pathogen data as part of existing national animal pathogen surveillance programs.

Such funding would also support exploration of accreditation and proficiency requirements to certify veterinary diagnostic labs (similar to CLIA for human health laboratories) to allow all farms and producers to better choose where they put their money and be guaranteed they are getting high-quality testing with accurate results. Maintaining and enhancing the veterinary diagnostic infrastructure is essential to improving antibiotic stewardship in the food animal industry. Enabling integration of national AST data on priority animal pathogens from multiple laboratories will contribute greatly to the national surveillance goals. Integration would help to generate the data used to develop appropriate breakpoints. However, integration does not ensure an affordable cost of the diagnostic for the end-user.

2.2 Research and Development

Issue Statement 1: Few tests rapidly identify pathogens or provide rapid susceptibility results in food animal medicine.

Currently, culture-based methods to identify bacterial pathogens and conduct susceptibility testing usually involve delays of 2 or more days after sample collection. In outbreak situations, delaying treatment until diagnostic results are confirmed may have serious consequences for animal health. Therefore, rapid testing technologies should provide an opportunity to advance antibacterial stewardship by enabling more informed decisions that benefit animal health and reduce inappropriate antibiotic use. To achieve these goals, the diagnostic turnaround time must be sufficiently short to materially impact the therapeutic decision, which depends highly on the clinical scenario. Required turnaround times may be less than an hour for emergency treatment of critically ill animals, whereas turnaround times of several hours or longer could still be helpful in situations in which mass medication is under consideration. Regardless, diagnostic tests that can be conducted in the field setting are needed. Many viral diseases in food animals impact animal health by predisposing them to secondary bacterial infections. Therefore, rapid tests that discriminate viral from bacterial diseases may have less application in food animals than in companion animals or humans.

The WG recommends the following:

- **Investment in research on diagnostics that rapidly identify pathogens in food animals or provide rapid susceptibility results directly from the clinical specimen in the field setting.**
- **Investment in translational research to adapt diagnostics platforms developed for humans to animals.** Affordable, reliable rapid diagnostic tests would facilitate antibiotic stewardship in any setting. It is likely that rapid testing technologies will be highly transferrable across human and veterinary medicine but would need to be customized for the bacterial pathogens associated with each host species. Within host species, it will be necessary to prioritize pathogens with regards to the relative information that the rapid testing could provide to clinicians. Given that the resources for animal research are small relative to human research, opportunities to adapt advances in rapid testing platforms for human pathogens to veterinary medicine should be sought.

Issue Statement 2: Novel diagnostics are needed to advance process control in the harvest and postharvest sectors of the food supply chain to reduce exposure risk.

Foodborne transmission is a key link between food animal antibiotic use and resistance in some human pathogens, most notably *Salmonella* and *Campylobacter*. The public health community has set goals for reducing the prevalence of foodborne bacteria resistant to critically important antibiotics (e.g.,

fluoroquinolones, third-generation cephalosporins, and macrolides). Foods of animal origin, although hygienically produced, are not sterile, and innovations such as pasteurization of milk have had profound public health benefits by reducing exposure risk to consumers. Similarly, regulatory changes in the Hazard Analysis Critical Control Point (HACCP) and Pathogen Reduction Act of 1996 have had demonstrable impact in improving the microbiological quality of meat at U.S. processing plants.

In addition to visual inspection for gross contamination, assessment of process controls in meat industries is largely based on culture-based testing of carcasses that must meet regulatory guidelines for microbiological quality. The advent of affordable, non-culture-based technologies, including real-time PCR, to monitor microbial contamination has the potential to provide more rapid and detailed information about food processing, which could be used to improve processes and reduce contamination risks. Such technology would not specifically address antibiotic resistance or stewardship but could have broader impact on infection prevention across the food industry.

The WG recommends the following:

- **Support for research to develop culture-independent methods for detecting microbial contamination of carcasses and meats as a tool for improved process controls.**

Issue Statement 3: Additional information is needed on AST for key animal pathogens, including validated clinical breakpoints.

Effective employment of AST in veterinary clinical practice depends in part on the extent to which in vitro AST results are used by veterinary practitioners. Standardized procedures for AST and criteria for determining susceptibility, or breakpoints, for animal pathogens are overseen by the CLSI. Although it publishes breakpoints for many drug–pathogen combinations, this ongoing task is incomplete. In some cases, breakpoints have not been established; in others, breakpoints for humans are used as proxies without validation in animals. The CLSI standards are widely used in U.S. diagnostic laboratories, but there are generally limited data on clinical outcomes related to AST of key animal pathogens, as they are not required in the regulatory process.

The WG recommends the following:

- **Research grants for the generation and integration of additional data necessary for CLSI to establish test methods, quality-control range data, and interpretive categories (i.e., breakpoints) for priority animal pathogens for which there are currently none available or where human breakpoints are used.** Gaps in knowledge can be addressed via the current CLSI processes, which depend on the availability of appropriate data.

2.3 Regulatory

There is no regulatory issue identified.

FDA has regulatory oversight of veterinary devices, including diagnostic tests, and can take regulatory action if a veterinary device is misbranded or adulterated. However, FDA does not require premarket approval for devices used in veterinary medicine. It is the responsibility of the manufacturer or distributor to ensure that animal devices are safe, effective, and properly labeled. The USDA CVB regulates veterinary diagnostic kits. However, tests developed and used in house by contract testing services are not endorsed or regulated by the CVB. Therefore, the use of veterinary diagnostics is essentially market-driven, with relatively few regulatory constraints.

2.4 Behavioral

Issue Statement 1: There is negligible evidence-based data about how veterinarians incorporate diagnostic testing in making decisions to employ antibiotic therapy.

To date, there has been little research on the prescribing behaviors of veterinarians in the United States, including how diagnostic testing is integrated into clinical decision-making. Better understanding of prescribing behavior norms is desired to design curricula and professional educational programs. Comprehensive study of all components of behavior of veterinarians related to prescribing antibiotics is warranted.

The WG recommends the following:

- **Support for research into therapeutic decision-making behavior in veterinary medicine, including the use of AST and the potential for rapid diagnostics.** Research into therapeutic decision-making in veterinary medicine might best be undertaken by multidisciplinary groups that include, for example, sociologists and veterinary professionals. Given the different cultures among food animal veterinarians and the nature of their relationships with clients, research efforts may be more fruitful if targeting a single species or industry within a species (e.g., dairy or beef). Obtaining a better understanding of current diagnostic approaches may provide some direction in defining areas in which rapid testing may be most beneficial, thereby informing priority areas for research.
- **Educational programs for veterinarians on the use and interpretation of diagnostic tests and stronger curricula and continuing education programs linked to antibiotic stewardship.** There are currently many such initiatives underway, including those of the American Association of Veterinary Medical Colleges. Such efforts will be enhanced by a stronger foundation of research on prescribing behaviors.

3. Incentives for Alternatives to Antibiotics for Disease Interventions in Food Animals

Alternatives to antibiotics are broadly defined as nonantibiotic products intended for disease interventions and can include categories such as microbial-derived products, phytochemicals, immune-modulating products, and nutritional supplements. This simplistic definition differs somewhat from that used by USDA because of the desire to be all-inclusive of innovation and application. Nonantibiotic products are becoming the preferred choice for some food animal producers to maintain animal health and reduce the need to use antibiotics to prevent or treat disease, thereby reducing selection for antibiotic-resistant animal pathogens and foodborne bacteria. Although many alternative products are currently on the market and available to food animal producers, additional effective options are needed. For this report, the WG focused only on alternative products as a means to prevent or treat animal diseases while noting the connection with stewardship and therapeutic antibiotics. Multiple external pressures, such as consumer preference and restriction on the use of medically important antibiotics, have diminished the market for antibiotics in food animals. Therefore, novel antibiotics were excluded from consideration by the WG because the established regulatory pathways and guidance for sponsors already exists. The development of these products remains an important priority to safeguard animal health while government agencies ensure their safety to public health. Incentives for research and development for nonantibiotic alternatives

for growth promotion were excluded from consideration by the WG because USDA is already engaged in this area.

3.1 Economic

Issue Statement 1: Funding is lacking to generate a sufficient pool of high-quality alternative candidates at the early and middle stages of R&D.

Animal health companies typically fund their own R&D programs but also invest in the acquisition of innovative technologies from academic and government research laboratories (i.e., public-private partnerships) and thus expect candidates for their pipeline of products to have a high probability of technical, regulatory, and commercial success to achieve ROI. Animal health companies therefore need a diverse and sufficient amount of “de-risked” candidates for acquisition to allow for a more competitive entry into the market place. De-risked candidates are those that have sufficient data on quality, efficacy, and safety to suggest likely success in reaching the market. However, acquisitions from public research institutions are often associated with uncertain technology transfer pathways and licensing agreements that may elevate risk. Currently, these risks and the limited funding and resources available for research into developing de-risked alternative candidates for disease intervention also limits the likelihood that a sufficient pool of high-quality alternative candidates will be available to enter the R&D process and finally reach the market place.

Furthermore, in large companies, alternative disease intervention products compete for funding and resources with product candidates in other areas of veterinary medicine (e.g., companion animal cancer or obesity and parasiticides). Therefore, alternative products are typically seen as providing a relatively lower ROI, which leads to less innovation and fewer resources dedicated to their development. To compensate, larger companies prefer to avoid investing in basic R&D by acquiring de-risked alternative candidates from startup companies, academic institutions, or other sources.

The WG recommends the following:

- **Initial funding for the Innovation Institute as per the National Policy.**
- **Enhanced support for small business innovation on alternatives through existing government programs (e.g., SBIR funding) and private-sector investment incentives.** Securing funding requires some degree of assurance that the investment (loan or other financing) will generate a gain (i.e., ROI) by an increased valuation and likelihood of future market success with a de-risked candidate. Recognizing the risk involved in extending financing in this area, appropriate adjustments might be considered, such as research tax credits for successful commercialization to offset anticipated losses or failures. This recommendation encourages ongoing public-private partnerships in which government incentives are leveraged with private business investment to share risk and reward.
- **Enhanced technology transfer pathways within the Innovation Institute.** Uniform and improved technology transfer pathways should be identified to de-risk the candidate product and increase investments and R&D collaborations between government research institutions and their commercial partners. Specific incentives to de-risk candidate products could include contribution of resources towards early-stage development, clear options for exclusivity for licensing and commercialization of government-owned inventions, and scientific support for pivotal studies for submission to regulatory agencies (i.e., FDA or CVB).

3.2 Research and Development

Issue Statement 1: Small companies, government agencies, and independent innovators do not have readily available resources to conduct key studies that de-risk alternatives.

Research on effectiveness of alternatives requires coordination of people, places, protocols, and procedures that is often beyond the capability of small-to-medium enterprises, university research centers, and other organizations that are typically laboratory-oriented. Obtaining experienced drug developers, such as disease specialists, pharmacologists, veterinarians, clinical microbiologists, and other disciplines, on an ad hoc basis is not efficient, nor is the identification of study sites, study protocols, and procedures.

In addition to resources, there is a lack of technical capability and support for early-stage development of alternative candidates. The conduct of effectiveness studies for alternatives for disease intervention is complicated by many technical factors (e.g., relevance of model studies versus field studies, ascribing nonspecific effects like immune support or intestinal health versus specific host immune potentiation to clinical outcomes, or direct versus indirect effects on bacteria) that should all be considered. Basic research is needed to define the mechanism(s) of action associated with clinical outcomes of innovative technology. Such research is critical to support the “proof-of-concept” stage for animal health products and underpins the demonstration of efficacy in the target animal species.

The WG recommends the following:

- **Support services provided by the Innovation Institute to connect innovators across sectors to the needed resources for R&D.** Practical and technical support would enhance connections between developers and contract research organizations, government agencies, consultants, experts, and mentors who can increase efficiency of the development process, thus reducing costly delays.
- **Specific solutions outlined in the National Policy to meet the needs and challenges of early developers.** The proposed policy would also facilitate training for a new cadre of developers and entrepreneurs to create a sustainable workforce.

Issue Statement 2: There is an incomplete understanding on how best to use an alternative product(s) in food animal production settings and how a new product can provide an added benefit compared with existing ones.

Comparing the effectiveness of an alternative product with an established product used for the same or similar indication or reason can be costly and challenging, but such data are pivotal to support decision-making by food animal producers and veterinarians. Clinical outcomes data on alternatives and data that support future comparisons to other product candidates are also needed to change purchasing and use decisions. (*See also Behavioral Issue Statement 2.*) Animal health companies are faced with the challenge of applying the data available to show purchasers the added benefit of their alternative product and, in turn, how food animal producers can maximize their benefits from the use of the product.

The WG recommends the following:

- **Grants to researchers or food animal production companies to conduct field studies using alternative products to establish optimal conditions of use and compare effectiveness with established products in their own production environment, with the condition that study**

data be entered into a central database so that others can benefit from the work. This approach offers producers the opportunity to try out a new intervention with less financial risk. A database repository may enable identification of trends and prioritization of studies to fund. However, the potential business risk to a manufacturer from a study that is interpreted as a “failure” (instead of a working estimate for comparison) may discourage use of this approach.

3.3 Regulatory

Issue Statement 1: Early-stage developers of alternatives face the challenge of determining which regulatory agency has jurisdiction over their candidate.

While FDA, CVM, and USDA provide guidance documents, researchers, small-to-medium companies, and startup companies do not have a simple mechanism for obtaining rapid, specific determinations as to which agency has regulatory oversight for their novel, alternative technology and what is required to advance those candidates. Basic research scientists and startup companies are typically resource-constrained and do not have drug development experts available to guide them on which agency has jurisdiction over their technology. Developers are limited by the effort and time of establishing initial connections with regulatory agencies to fully understand the procedures and requirements of each. Obtaining decisions specific for their candidate—such as the need for regulatory approval or how the unique nature of the candidate may complicate studies on safety, quality, or effectiveness—is not always clear-cut, which hinders ascertainment of the pros and cons of advancing their candidate and can be inefficient and costly for innovators.

The WG recommends the following:

- **The proposed Innovation Institute to serve as the single point of contact for basic research scientists and small companies to facilitate and obtain feedback from CVM and USDA.** This “one-stop shop” approach would bring together current jurisdictional agency efforts underway, centralizing them under a single, coordinated entity as the initial point of contact. This model would also bolster current cross-agency efforts to provide information and advice in a more efficient manner while decreasing the likelihood of misinformation or confusion. Expedient responses to inquiries are the desired outcomes for innovators who seek clarity on regulatory requirements; the information gained is fundamental to planning, budgeting, and valuation for small-to-medium enterprises. As an added benefit, the centralized Innovation Institute approach will increase education and awareness for scientists and others on the regulatory requirements, which can then contribute to improvement of workforce productivity and commercialization efforts.

Issue Statement 2: There is no standardized regulatory guidance for developers of alternatives because of the diversity of types of alternative products, thus there is a need for flexibility to generate the necessary data for review.

In some situations, the current regulatory guidance was written for antibiotics. Applying the guidance to nonantibiotic alternatives creates challenges to study designs unless the guidance is acceptably modified to be “fit for purpose.” For example, a new immune-modulating compound was developed to prevent infections that lead to bovine mastitis. However, CVM guidance recommended demonstration of treatment of acute mastitis before the product could be considered for a prevention indication. Ultimately, the compound was approved through a modified interpretation of the guidance appropriate to the technology. Without flexibility by CVM, the developer would have been unable to meet the recommended level of effectiveness.

The anticipated new technology for alternatives will likely require equally novel regulatory approaches. Of course, not all alternatives will need regulatory approval, but for those that do, the agency guidelines may need to be flexible or adapted to meet specific needs. To enable data to be generated that addresses the spirit and intent of existing guidance without having to revise the data for a specific circumstance will require regulatory staff to consider using innovative methods or approaches. Regulatory staff can enhance their scientific knowledge through education and scientific meetings, for example, which will result in more flexibility for unique situations and speed up timelines for innovators. However, such an effort requires the appropriate resources and expertise on knowledge management (i.e., internal sharing within and across agencies) to prevent silos.

Alternative products should not contribute to antibiotic-resistant bacteria prevalence or otherwise contribute to an undesired effect. This aspect is typically taken into account for products for which regulatory approval is sought. However, regulatory agencies should consider revisiting the matter as part of their ongoing explorations of novel technology.

The WG recommends the following:

- **Ongoing exploration of novel technologies (e.g., via education, scientific meeting attendance, expert consultations, workshops, cross-agency exchanges, or in consultations with counterpart regulatory agencies in other countries) to inform CVM and USDA efforts to find new ways of satisfying evidentiary requirements through innovative regulatory approaches appropriate for the alternative candidates.** Such efforts should include close collaboration or consultation with regulatory counterparts in FDA centers responsible for human drug development and regulatory agencies in other countries.

3.4 Behavioral

Issue Statement 1: Researchers lack awareness of the business value and process of patenting novel technology (to protect IP), which may result in public disclosure (e.g., via publication), thereby diminishing the value of the technology.

Research scientists would benefit from an awareness of the value and reward of IP protection. Typically, patenting is not thought of on the same level as publications or other accomplishments. The increase of patented technology can help create a sufficient pool of alternatives to antibiotics at the earliest stage when innovative candidates are discovered.

Companies highly value IP protection for new technology and require it before considering other aspects of an early-stage candidate for investment, so having a larger pool of technologies available initially is essential. Innovators have a year following publication of their own work to file for a patent, so although companies may prefer that there be no prior disclosure, publication and patent protection can coexist. There is a need to change the behavior and mindset of researchers and scientists to that of preserving the IP (i.e., provide an incentive for patenting).

The WG recommends the following:

- **Awareness of the need and process for initiating patent protection of new technologies, included as part of the educational resources and outreach efforts of the proposed Innovation Institute.** Awareness in itself can serve as an incentive for increased IP protection for institutions, companies, or individual researchers studying novel nonantibiotic interventions.

It is envisioned that information and general direction on the process of patenting would be available as a resource to innovators to enable them to understand the importance of and pathway to patenting for new technology as a business service, in alignment and connection with the U.S. Patent Office. Only direction would be provided, not specific legal advice.

- **Additional incentives for early-phase innovators or organizations could also include patent application fee reimbursements or postpatent award or fee waivers to encourage submissions.** Because IP is a leading indicator of commercialization potential, an entrepreneurial mindset of new technology must be extended to researchers unaware of its value, with information facilitated through the Innovation Institute to provide a convenient point of contact. Such efforts require additional resources; therefore, exploration of funding sources or a budget for reimbursements is needed.

Issue Statement 2: Stakeholders have not fully accepted alternatives to antibiotics because they lack trust in their effectiveness and safety.

Food animal production companies, food retailers, food service companies, veterinarians, and consumers have not yet fully accepted and transitioned to the use of alternatives as nonantibiotic disease interventions for food animals because of apprehension about unintended or unforeseen consequences that could be detrimental to animals, business, or brand. Many stakeholders currently have an expectation that alternatives should provide the same level of effectiveness as antibiotics, but at a reduced cost and without resistance concerns. This expectation may contribute to a lack of understanding of how alternatives can best be used to help prevent (or treat) infection without jeopardizing animal health or welfare and food safety or public health.

Additionally, a company must consider how use of an alternative could influence its brand. Decision-makers typically take an evidence-based mindset to overcome apprehension regarding the use of new products. Thus, to change behaviors, key influencers need data upon which they can base their decision-making. (*See also R&D Issue Statement 2.*) Those who are convinced of the benefits of alternatives can help promote the approach to colleagues. This strategy should actively incorporate existing food animal production advisors, such as university extension agents, company technical representatives or nutritional specialists, and others who already have the trust of the key decision-makers for a specific food animal production operation.

The WG recommends the following:

- **Analysis of information gathered in the proposed database repository from alternative product studies to assess health outcomes and possibly affected business aspects (e.g., ROI).** Analysis can be conducted within the proposed Innovation Institute, in partnership with appropriate participants from the private sector. Although study design is an R&D matter, the calibration of results from food animals produced with alternatives to food animals produced with therapeutic antibiotics can contribute to better antibiotic stewardship. Because data drive decision-making on new product adoption practices and interventions, local, on-farm studies demonstrate relevance and increase confidence in and communication of adoption of new practices, which is key to expanded implementation. The technical analytical capability needed, however, may be complicated by study designs, confidentiality issues, or potential negative business impact for products that do not perform to expectations. A standardized protocol for analysis with such implications must be taken into consideration.

GLOSSARY OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AHRQ	Agency for Healthcare Research and Quality
AIF	antibiotic incentive fund
AMR	antimicrobial resistance
ARLG	Antibacterial Resistance Leadership Group
AST	antimicrobial susceptibility test
BARDA	Biomedical Advanced Research and Development Authority
BIO	Biotechnology Innovation Organization
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CLSI	Clinical and Laboratory Standards Institute
CMS	Centers for Medicare and Medicaid Services
CRE	carbapenem-resistant Enterobacteriaceae
CVB	Center for Veterinary Biologics
CVM	Center for Veterinary Medicine
DISARM	Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (Act)
DoD	U. S. Department of Defense
DRIVE-AB	Driving Reinvestment in R&D for Antibiotics
FDA	Food and Drug Administration
G20	Group of 20
GAIN	Generating Antibiotic Incentives Now (Act)
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HACCP	Hazard Analysis Critical Control Point
HHS	Department of Health and Human Services
IDSA	Infectious Diseases Society of America
IP	intellectual property
IRB	institutional review board
LPAD	limited population antibacterial drug
MALDI-TOF	matrix-assisted laser distortion/ionization-time of flight
MER	market entry rewards
MIC	minimum inhibitory concentration
MMWR	<i>Morbidity and Mortality Weekly Report</i>
NAAT	nucleic acid amplification test
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OIE	World Organization for Animal Health
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PCORI	Patient-Centered Outcomes Research Institute
PCR	polymerase chain reaction
PDUFA	Prescription Drug User Fee Act
PhRMA	Pharmaceutical Research and Manufacturers of America
R&D	research and development
READI	Reinvigorating Antibiotic and Diagnostics Innovation (Act)

ROI	return on investment
RSV	respiratory syncytial virus
SBIR	Small Business Innovation Research
USDA	U.S. Department of Agriculture
USG	U.S. government
WG	[PACCARB] Working Group