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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*,¹ 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) comprising federal and council member subject matter experts in both human and animal domains to address incentives for developing vaccines, diagnostics, and therapeutics (for humans) or alternatives to antibiotics (for animals). 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 draft report, they are defined as follows:

- **Economic:** Issues that influence the ROI to companies 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, and 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 as such in the text.

Before attempting to generate recommendations, the WGs wanted to better understand the primary issues driving the lack of investment in and corresponding development of vaccines, diagnostics, and therapeutics/alternatives. This report represents the WGs' progress in identifying issues. It does not reflect the full PACCARB's opinions, nor does it include final recommendations.

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 Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), the Department of Agriculture (USDA), the National Institutes of Health (NIH), and the Biomedical

¹ Initial Assessments of the National Action Plan for Combating Antibiotic-Resistant Bacteria:
<https://www.hhs.gov/sites/default/files/paccarb-final-report-03312016.pdf>

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Advanced Research and Development Authority (BARDA). 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 House²
- Duke University's Margolis Center for Health Policy³
- United Kingdom UK AMR Review/O'Neil Group⁴
- Driving Re-Investment in R&D and Responsible Antibiotic Use (DRIVE-AB) consortium⁵
- Pew Charitable Trust, Infectious Diseases Society of America, and the Pharmaceutical Research and Manufacturers of America (PhRMA)⁶

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

This report is organized in two main sections: human health and animal health. Each section describes in brief the issues identified for vaccines, diagnostics, and therapeutics/alternatives, respectively. The WGs have discussed ways to address the issues, but have not yet reached consensus on recommendations. The final report, with recommendations that reflect the consensus of the WGs, will be presented for a vote at the September 2017 PACCARB meeting.

² Chatham House Report: Towards a New Global Business Model for Antibiotics: Delinking Revenues from Sales. October 2015.

https://www.chathamhouse.org/sites/files/chathamhouse/field/field_document/20151009NewBusinessModelAntibioticsCliftGopinathanMorelOuttersonRottingenSo.pdf

³ *In progress*

⁴ Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. May 2016. http://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

⁵ Incentives to stimulate antibiotic innovation: The preliminary findings of DRIVE-AB. June 2016. <http://drive-ab.eu/wp-content/uploads/2016/06/WP2-Prereading-FINAL.pdf>

⁶ Reviving the pipeline of life-saving antibiotics: Exploring solutions to spur innovation. September 2011. http://www.pewtrusts.org/~media/legacy/uploadedfiles/phg/content_level_pages/issue_briefs/AIPPipelineProceedings9webpdf.pdf

Section I. Human Health

The financial and regulatory incentives needed to address the lack of development of products to combat antibiotic resistance vary and will require investment from public and private entities. The market forces that affect vaccines, diagnostics, and therapeutics are very different and thus require individualized approaches to spur investment. Examples of such measures include, but are not limited to, 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 of the previously published reports recommend some sort of combination of push and pull incentives, including the recent work conducted by the Duke-Margolis Advisory Group on U.S. payment models for effective antimicrobial development and use. Push incentives include grants, contracts, and tax credits during the development phase while pull incentives such as prizes, market exclusivity, and downstream financial rewards come into play after approval of the respective product. There are pros and cons of each approach. Therefore, several types of push and pull incentives will be discussed in the following three sections on human health.

1. Incentives for Vaccines for Human Use

Vaccines for humans may target resistant pathogens directly (AMR vaccines) or indirectly by reducing the incidence of infections for which antibiotics are prescribed inappropriately (indirect AMR vaccines). Examples of indirect AMR vaccines include influenza vaccines, which reduce upper respiratory infections, and respiratory syncytial virus vaccines in development. However, vaccines face behavioral, economic, and legislative 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. Such vaccines could address 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 included in legislation that incentivizes the development of AMR products. The GAIN⁷ Act and current drafts of the proposed DISARM⁸ and READI⁹ Acts do not include incentives for prophylactic interventions. The exclusion of incentives for prophylactic AMR products is a further barrier to development of AMR vaccines, some of which have already demonstrated tremendous value in reducing AMR (e.g., *Haemophilus influenzae* type B and pneumococcal vaccines).

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 directed at AMR pathogens. (1)

While there is widespread recognition of the value of vaccines for the pediatric population, the understanding of their relevance in adults is not as well established among stakeholders, whether focused on routine vaccine-preventable infections or those associated with resistant pathogens. An essential aspect of properly positioning vaccines as an element of a larger U.S. response against AMR is to generate data that documents how such vaccines—existing or potential—can impact society favorably. Such data can then inform supportable investment and incentive strategies.

⁷ Generating Antibiotic Incentives Now Act 2012

⁸ Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms Act

⁹ Reinvigorating Antibiotic and Diagnostic Innovation Act

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

Only large pharmaceutical companies can absorb the risks and costs to sustain end-to-end development of infectious disease vaccines. Smaller companies and other organizations find it exceedingly difficult to raise sufficient capital to develop needed vaccines, especially those utilizing novel technologies or focused on new targets. The lack of capital means that vaccine research by academics, government bodies, and nongovernmental organizations may not be translated to smaller biotechnology companies, leading to further erosion of the early-stage pipeline of AMR vaccines.

1.2 Research and Development

Issue Statement 1: There are insufficient epidemiological data on antibiotic use due to infections caused by pathogens currently or potentially preventable through vaccination. (3)

Additional understanding is needed about how much inappropriate use of antibiotics is attributed to treating vaccine-preventable conditions. Data from surveillance can inform vaccine development and deployment strategies by enhancing the use of vaccines.

Issue Statement 2: The clinical-stage pipeline for vaccines against AMR pathogens is weak. (4)

By definition, vaccine development is a form of public health R&D. In general, most vaccines focus on large populations at risk (e.g., pediatric combination vaccines, influenza vaccine, and hepatitis B vaccine). Vaccines specifically for AMR pathogens have a more limited target population, making it more of a challenge for a developer to commit to a sustained development effort that may last more than a decade, involve great costs, and have a very limited (or no) ROI. The public health value of these “niche” vaccines remains important, however. 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.

1.3 Regulatory

Issue Statement 1: 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). (5)

Vaccine development sponsors routinely interact with FDA to shape development plans, identify clinical trial endpoints, and align the science with likely indications for use. The process is further complicated by the need for ACIP review after the vaccine is approved by FDA. The ACIP is a federal advisory committee, and its recommendations weigh heavily on the final use recommendations issued by CDC. While it would be inappropriate for the ACIP, FDA, or any other entity involved in a regulatory process to preordain an approval, the lack of clarity about the ACIP review process and the criteria for vaccine recommendations remains an area of uncertainty for vaccine developers. A more codified consultative process with either the ACIP or CDC, analogous to the routine consultations that occur with FDA, would give vaccine developers a reasonable understanding of how their vaccines will be reviewed and the types of data that will be important for this review.

Issue Statement 2: The lack of clarity about regulatory pathways for vaccines focused on AMR pathogens reduces the willingness of sponsors to produce vaccines. (6)

The regulatory process for large, population-focused vaccines (e.g., influenza and pediatric vaccines) is well defined. Whether via well-accepted serology endpoints, comparison with other approved vaccines, or actual efficacy studies, developers have a clear understanding of how these vaccines should move through the regulatory process. Vaccines intended to prevent AMR-associated infections may face a much more challenging path to approval and use if they target specific, smaller, at-risk populations or relatively uncommon pathogens. Vaccine developers need more information about how best to develop such vaccines and what mechanisms or pathways are available so they can frame their plans for a successful regulatory submission.

1.4 Behavioral

Issue Statement 1: Implementation strategies for optimal vaccine acceptance and utilization are inadequate. (7)

Current evidence about the benefits of vaccines is underutilized. Many providers (non-pediatricians) do not consider vaccination strategies as part of their routine delivery of healthcare. Additionally, the general population does not understand or appreciate the value of vaccines in prevention of disease, especially adult vaccines. An evidence-based comprehensive strategy that targets, primarily through education, healthcare providers and the general public is needed.

Issue Statement 2: Providers lack knowledge about the role of vaccines in preventing AMR. (8)

While the use of vaccines in pediatrics is well understood, providers are less clear about how vaccines can positively impact the incidence of AMR-associated infections, especially among adults. For example, effective use of influenza and pneumococcal vaccines in adults can have a significant impact on the inappropriate use of antibiotics, yet health care providers who treat adults often do not consider this aspect of preventive medicine.

2. Incentives for Diagnostics for Human Use

Used to inform appropriate antibiotic prescribing, diagnostic tests can reduce hospital lengths of stay, prevent hospital admissions, reduce antibiotic use, and benefit society by curtailing AMR. However, adequate diagnostic tests do not exist that match the clinical needs of inpatient and outpatient settings, which stems from problems related to both the development and limited use of diagnostics. 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 useful in typical office or clinic settings (e.g., provide results in 10-15 minutes) and 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 document addresses the following: 1) antimicrobial susceptibility test (AST) devices for new antibiotics, 2) rapid tests that distinguish between bacterial and viral infections, and 3) tests that can quickly identify bacteria and allow for rapid susceptibility testing. Each of these tests is used in different clinical settings.

2.1 Economic

Issue Statement 1: There is a delay in availability of ASTs for newly approved antibiotics. (9)

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. Prior to 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. 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. Under the current regulatory system, it may 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. The availability of a rapid AST, such as an Etest or an antibiotic disc, when the antibiotic is approved would greatly improve the ability of laboratories to provide critical information.

Issue Statement 2: Because there is no method to determine the value of a diagnostic test, reimbursement is not aligned with the value of the diagnostic test. (10)

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. The inability of a laboratory to recoup the cost of the test acts as a major disincentive to provide it for clinicians. Currently, reimbursement for 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 in 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 a test. An approach where reimbursement could be supplemented for tests that detect, quantify, or characterize pathogens of major public health importance could drive test development and implementation.

Issue Statement 3: There is a lack of clinical and economic outcome studies showing that diagnostic tests prevent the emergence of antibiotic-resistant bacteria and are cost-effective. (11)

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 do not exist, 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 add cost 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.

Issue Statement 4: The high cost of development of diagnostics is a disincentive for diagnostics companies. (12)

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 both public health concerns 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. Costs are increasing at a rapid pace because of the need for better technologies and new platforms, need for complex clinical outcomes studies, and use of health technology assessments.

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. (13)

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 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. (14)

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 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. (15)

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 both 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.

Issue Statement 4: Collaboration between diagnostics companies and other stakeholders is limited and inconsistent. (16)

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.

2.3 Regulatory

Issue Statement 1: The regulatory approval clearance process for modifying and improving existing diagnostic tests is complex and expensive. (17)

One of the major barriers to improving a test, once it is FDA-cleared, is the regulatory requirements. 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 expense for companies, and it is 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. Thus, companies have little incentive to make these improvements. As a result, clinical laboratories often use out-of-date technologies or tests with less than ideal performance characteristics for years.

Issue Statement 2: The current regulatory process for new diagnostics is time-consuming and costly, posing a disincentive for developers. (18)

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 (e.g., 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.

Issue Statement 3: There are no requirements for hospitals to update their microbiology laboratories with newer technologies. (19)

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 *Staphylococcus aureus* and coagulase-negative staphylococci provide therapeutic information within an hour or two after the blood culture becomes positive that 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.

2.4 Behavioral

Issue Statement 1: Clinicians do not always use diagnostic tests, believe the results, and act on them. (20)

Limited use of diagnostics, especially in the outpatient setting, stems from the lack of a 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.

3. Incentives for Therapeutics for Human Use

Although USG efforts to date have been supportive, incentivizing development of innovative therapeutics to address antibiotic-resistant infections and reversing the current market failure in antibiotic R&D will require transformative measures.

Taken together, these changes should 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 lower than for most other drugs. (21)

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. Due to 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.

3.2 Research and Development

Issue Statement 1: Finding molecules that kill bacteria without also harming the patient is scientifically challenging. (22)

Nearly all antibiotics currently available for patients are based on discoveries initially made over 30 years ago.

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. (23)

Infections due to rare and/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--if not impossible--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.

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. (24)

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. (25)

Sponsors of narrow-spectrum agents face an additional struggle in that low rate of occurrence of infections caused by specific target pathogens (whether resistant or 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 Regulatory Issue Statement 2*).

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. (26)

Models of care and alternative payment models are evolving.

Section II. Animal Health

Antibiotics have been important tools for combatting bacterial infections in livestock, poultry, and companion animals for over 60 years. The contribution that the administration of antibiotics to animals makes to the problem of antibiotic resistance in medical settings remains to be quantified. It is widely acknowledged that selective pressures from antibiotic use in any setting will augment the resistance challenge, and all opportunities to replace or refine 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 array of environments in which domesticated animals 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/alternatives are different between companion animals and animal agriculture. Therefore, to appropriately limit the scope of the incentives 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. 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 side effects on other bacteria that may be present, including foodborne pathogens such as salmonellae or *Campylobacter*, and the downstream effects of treatment choices on the consumer and the environment.

Population health management encompasses all factors that impact animal health, including housing, genetics, nutrition, and management in addition to core veterinary activities such as vaccination, disease diagnosis, and therapy. The growing demand for foods derived from animals raised without antibiotics leads to increasing adoption of strategies that reduce the need for antibiotics. However, because of animal disease outbreaks, antibiotics will continue to play an important role in maintaining animal health and well-being on the majority of farms.

Another unique consideration for the food animal industry is that producers absorb the cost of medications or interventions and, unlike insurance companies in human health, there is generally no reimbursement for any of the costs of interventions. Thus, the sale of animals at market is the most realistic way to assess the ROI for the intervention used. The ROI can be measured by performance parameters such as feed consumption/efficiency, daily weight gain, time to reach market weight, and decreased death loss.

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,^{10,11} in addition to a

¹⁰ FDA Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals. April 2012.
<https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf>

¹¹ 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.

growing consumer preference for food raised without antibiotics, contribute to the current trend of using fewer antibiotics in animal agriculture. Under a One Health approach, animal production practices should not only benefit animal health and welfare but food safety and public health as well. However, in order to reduce reliance on the use of medically important antibiotics in animal agriculture, alternative products that contribute to disease intervention are needed along with improved diagnostic tools.

When viewing the problem of AMR from a One Health perspective, a consistent concern is the unequal allocation of funding for research in animal health compared with human health. The threat of AMR clearly demonstrates the need for a cooperative approach between animal and human health sectors, because resistant bacteria can be shared among species. Yet, there are far fewer resources allocated for AMR issues in animal health than are needed. The WGs see potential for agencies that deal with human health concerns of zoonotic bacteria also consider funding projects related to animal health as another means to reduce human disease, and specifically, infections caused by AMR bacteria of animal origin.

Given the need for innovation to combat antibiotic-resistant bacteria, the time is right to stimulate the development of novel approaches that will reduce the need for antibiotic use in animals and make necessary uses more strategic and effective. The ultimate benefit will be to improve food safety and public health for the U.S. workforce, stimulate new business opportunities to ensure agricultural competitiveness, and ensure a sustained scientific and regulatory workforce for the future.

The topics of vaccines, diagnostics, and alternatives will be addressed individually, but an overarching recommendation for all three is the creation of an Innovation Institute and a corresponding national policy on alternatives to antibiotics for food animals to guide the scope and emphasis of the Innovation Institute. The proposed Innovation Institute would serve as an entrepreneurial coordinating and resource center for all aspects of novel technology development and implementation. It would provide resource services that support animal health and welfare as related to disease prevention and treatment, including the use of diagnostic tools, antibiotic stewardship, and food animal production practices. The Innovation Institute would complement ongoing activities within USDA, FDA CVM, and other agencies (BARDA, NIH, CDC, U.S. Agency for International Development [USAID], DOD, U.S. Patent Office, etc.) and establish connections with veterinary medical organizations, animal health companies, associations (e.g., Animal Health Institute, Kansas City Animal Health Corridor), food animal production companies, universities, contract research organizations, regulatory consultancies, scientific associations, biotechnology organizations (e.g., Biotechnology Industry Organization), and perhaps funding organizations (Gates Foundation, venture capital companies, etc.).

Put simply, the Innovation Institute would be a “one-stop shop” for researchers, small-to-medium enterprises, startups, universities, and others with technology to develop for initial commercialization in the United States. The available resource connectivity would also be valuable to One Health efforts for translation studies using animal models for human disease or as a pathway for molecules no longer of interest for human health. The Institute would be embedded within USDA, perhaps at a physical site, and would support intramural and extramural research. The work of the Institute would not be only at the level of bench or field research but also its work would be accomplished virtually and through outreach.

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, the idea of how to incentivize new vaccine development and use is a novel concept for agriculture. Currently, there are research programs in place at USDA for development of new vaccines for catastrophic diseases, such as influenza or foot and mouth, as well as limited vaccine discovery research programs for the more common diseases faced during the production cycle. Thus, public-private partnerships are important to advance the 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/or deliverable through mass vaccination) in animal production. An important factor is that developers and users are deciding what vaccines to market or use based on economic drivers.

There are two ways in which vaccine use in animal agriculture could reduce the emergence and spread of AMR bacteria. 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*, salmonellae, and enterococci). This approach would prevent these bacterial pathogens from being introduced into the human food supply and causing severe illness in humans via contaminated food products from animals, and as a result, reduce the need for and the amount of antibiotics used to treat people.

Like all interventions in animal agriculture, the cost of the intervention is borne, 100%, by the farmers. This is the reason why animal vaccines targeted to bacteria that are pathogenic to humans, but not to the animal, are not economically viable unless the farmer is compensated for their use of the vaccine. 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 even if they do not deliver tangible benefits to farmers 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. (27)

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, farmers 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 AMR¹²). 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.

1.2 Research and Development

¹² https://www.cdc.gov/drugresistance/biggest_threats.html

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. (28)

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.

Issue Statement 2: Vaccine delivery systems for mass vaccination are not optimized for specific animal-pathogen-production scenarios. (29)

Routes of vaccine administration vary depending on the species, the pathogen, or the production setting. Some vaccines are administered to individual animals via injection, but a critical gap for intensive animal production systems such as aquaculture or poultry production 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, particularly how to overcome challenges to mass-vaccination (e.g., through addition to drinking water). Also, R&D must incorporate advancements in adjuvants, formulations, and host immune system understanding.

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. (30)

Epidemiological studies and models are needed to show how a vaccine will 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 what vaccines to use.

1.3 Regulatory

Issue Statement 1: Regulatory processes prevent a flexible approach and rapid approval of vaccine strain updates in vaccine development. (31)

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 guidance¹³ indicates that strains within equine and swine influenza vaccines can only be updated after demonstration of a reasonable expectation of 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 and welfare with ROI. (32)

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.

¹³ Veterinary Services Memorandum 800.111, https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_111.pdf

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, 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. Generally, more rapid and affordable diagnostics would advance antibiotic stewardship in food animals worldwide.

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. (33)

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. Although treatment is moving toward more evidence-based approaches, 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.

Issue Statement 2: The use of diagnostic testing can be limited by the expense incurred. (34)

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 is highly variable among clinical settings, as is 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.

2.2 Research and Development

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

animal medicine. (35)

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 this, the diagnostic turnaround time must be sufficiently short to materially impact the therapeutic decision, which will be highly dependent 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 where 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.

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. (36)

Foodborne transmission is a key link between food animal antibiotic use and resistance in some human pathogens, most notably salmonellae 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.

Issue Statement 3: Additional information is needed on AST for key animal pathogens, including validated clinical breakpoints. (37)

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 is generally limited data on clinical outcomes related to AST of key animal pathogens, as they are not required in the regulatory process.

2.3 Regulatory

Issue Statement: 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. (38)

To date, there has been negligible research of prescribing behavior 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.

3. Incentives for Antibiotic Alternatives for Animal Use

Alternatives are broadly defined as nonantibiotic disease interventions and can include categories such as microbial-derived products, phytochemicals, immune-modulating products, and nutritional supplements. They 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 options are needed for the various animal species that are more consistently effective and field-evaluated for optimal efficacy. For this report, the WG focused only on alternatives and their relationship to stewardship of 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. Incentives for research and development for nonantibiotic alternatives for growth promotion were excluded from consideration by the WG because the USDA is already engaged in this area.

3.1 Economic

Issue Statement 1: Funding is lacking to generate a sufficient pool of quality alternative candidates at the early and middle stages of R&D. (39)

Animal health companies typically fund their own R&D programs, and thus expect candidates for the pipeline of products to have a high probability of technical, regulatory, and commercial success to achieve ROI. Larger companies 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. Currently, 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 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.

Issue Statement 2: Many alternatives on the market do not have efficacy data comparable to that of antibiotic products, yet they are preferred by food animal producers over more expensive antibiotics or alternatives that have proven effectiveness via a regulatory approval process. (40)

Companies developing alternative product candidates may either seek regulatory approval for a particular indication or they may choose to demonstrate safety only. The regulatory pathway drives R&D costs. Approved products are likely to be more expensive for producers and veterinarians than alternatives that have a designation of “generally recognized as safe” (GRAS) or have otherwise demonstrated safety. The cost differential may discourage companies from seeking regulatory approval to be competitive in the market place. Looking at it another way, the anticipated higher price projection for new products that will have a regulatory approval and label indication means they are not as likely to gain sufficient market share and achieve the desired ROI by the manufacturer, which in turn may decrease the likelihood of an initial R&D investment.

3.2 Research and Development

Issue Statement 1: Small companies and independent innovators do not have readily available resources to conduct key studies that de-risk alternatives. (41)

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 on 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 may require new approaches and evaluation paradigms.

Issue Statement 2: Due to insufficient comparative data for alternatives and antibiotics, 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 to the existing ones. (42)

Comparing the effectiveness of an alternative product to 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.

3.3 Regulatory

Issue Statement 1: Early-stage developers of alternatives face the challenge of determining which regulatory agency has jurisdiction over their candidate. (43)

While FDA's 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 for 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.

Issue Statement 2: There is no standardized regulatory guidance for developers of alternatives because of the diversity of types of alternative products. (44)

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 recommends demonstration of treatment of acute mastitis before the product was considered for a prevention indication. Ultimately, the compound was approved through a modified interpretation of the guidance appropriate to the technology. Without flexibility from 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 to secure a 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 it 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.

3.4 Behavioral

Issue Statement 1: Researchers lack awareness of the business value and process of patenting novel technology (to protect intellectual property [IP]), which may result in public disclosure (e.g., via publication), thereby diminishing value of the technology. (45)

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. The need is to change the behavior and mindset of researchers and scientists to that of preserving the IP (i.e., provide an incentive for patenting).

Issue Statement 2: Stakeholders have not fully accepted alternatives to antibiotics because they lack trust in their effectiveness and safety. (46)

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 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. These decision-makers typically take an evidence-based mindset to overcome apprehension regarding the use of the new products. Thus, to change behaviors, these 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.