National Antimicrobial Resistance Monitoring System (NARMS) Program Review

Conducted by:

External Subcommittee of the
Food and Drug Administration (FDA) Science Advisory Board

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EXECUTIVE SUMMARY

A group of common themes emerged from the deliberations of the NARMS Subcommittee. These themes included: (1) the need for an improved, statistically valid, and rigorous sampling strategy; (2) timeliness of reporting and reports; (3) harmonization of data; and (4) the creation of a contemporary surveillance platform that would enable participants to conduct hypothesis-driven research, add value, and improve the utilization of data to better achieve the objectives of the NARMS program.

In addressing the four specific questions posed to the Subcommittee, another group of key findings were developed that included the following: (1) The current group of sampling strategies for the various components of NARMS were all found to have degrees of bias. Thus, there is a need to transition these strategies to a group of national, random sampling strategies, including a methodology to better assess antimicrobial resistance in the intestinal flora of truly healthy individuals. When not feasible, data should be further stratified, or sampling should be limited and focused on specific hypothesis-driven research; where sampling biases cannot be corrected, the methodology should be designed as an early warning system for emerging resistance. (2) The Subcommittee strongly encouraged the further development and expansion of a NARMS research portfolio with an emphasis on hypothesis-driven and more collaborative research; there should also be a special emphasis on elucidating the mechanisms of transportation of resistance genes and bacteria across the farm-to-fork continuum and the resultant human infections and illnesses. (3) There was unanimity in support of creating a real-time, web-based, integrated database that would permit generating both participant-specific and collective reports and analyses. In addition, reports must be more timely and accessible, yet they must also be able to accommodate potentially confidential data such as when data on drug usage and exposures are captured in the future. (4) The Subcommittee concluded that the global expansion of NARMS or NARMS-type programs is a critical imperative. Antimicrobial resistance is a growing global issue that demands more international training and intervention; the NARMS program could be used as a model activity for international organizations and other countries.

The Subcommittee was especially pleased with the progress and growing acceptance of the NARMS program over the last decade. The program has evolved into a mission-critical tool for FDA, and the collaborative relationship among the agency participants is an excellent model for other government programs. New pilot projects have proven worthwhile and merit further development, and the on-farm data can help to better link the human and animal health interface and benefit both. The Subcommittee believes that the NARMS activities deserve to be considered as high priorities as agencies struggle with difficult funding decisions. In addition to addressing the pertinent findings, the Subcommittee strongly believes that the NARMS participants should develop an aggressive 10-year plan with new stretch goals using wide public involvement. It is an appropriate time to not only consider program improvements, but to also consider a longer planning horizon to ensure that the NARMS program becomes more strategic, encompassing, and commensurate with the growing global problem of antimicrobial resistance and future animal and public health risks and challenges.

Summary of Charge

The Science Board Advisory Committee to the Federal Drug Administration (FDA) established a subcommittee to evaluate the National Antimicrobial Resistance Monitoring Systems (NARMS) program and to address four questions relevant to the continued success of the program. The four questions included the following:

1. Are there inherit biases in the sampling strategies employed in NARMS? If so, how can they be improved to ensure that the data and interpretation are scientifically sound given current resources?

2. Are there epidemiological and/or microbiological research studies that would better serve the goals of NARMS and the regulatory work of FDA?

3. Are current plans for data harmonization and reporting appropriate? If not, what are the top priorities for advancing harmonized reporting?

4. Are the current NARMS international activities adequate to address the worldwide spread of antimicrobial-resistant food-borne bacteria?

Panel Approach

The Subcommittee (members listed in Appendix 1) met on April 10-11, 2007, in Rockville, Maryland, and heard presentations from the three federal partners of NARMS: FDA, Centers for Disease Control and Prevention (CDC), and United States Department of Agriculture (USDA). (Federal agency presenters are listed in Appendix 2). In addition, the Subcommittee also heard presentations from members of the public during a public hearing held as part of the program review (public presenters are listed in Appendix 3). This report will be submitted to the FDA Science Advisory Board on June 14, 2007, for their review and disposition.

Introduction

NARMS is a national collaborative network involving the FDA, CDC, and USDA. The system was developed to monitor changes in susceptibility/resistance of select zoonotic bacterial pathogens and commensal organisms recovered from animals, some retail meats, and humans to antimicrobial agents of public health and animal health significance.

NARMS was started in 1996 in response to a public health concern based on the recognition of the growing problem of antimicrobial resistance. The system has evolved over the last decade growing in stature, awareness, and importance. It has matured over the years and has undergone a series of changes and improvements based on continuous

challenges at the interface of human and animal health and the need to assess and monitor the occurrence of antimicrobial resistance in bacteria from animals, foods, and humans.

The goals of the NARMS program are:

1. Provide descriptive data and trends on antimicrobial susceptibility/resistance patterns in zoonotic, food-borne bacterial pathogens, and select commensal organisms;

2. Respond to unusual or high levels of bacterial drug resistance in humans, animals, and retail meats in order to contain or mitigate resistance dissemination;

3. Design follow-up epidemiology or research studies to better understand the phenomenon of resistance; and

4. Assist the FDA in decision making for approving safe and effective drugs for humans and animals, as well as promote prudent and judicious use of antimicrobials.

General Considerations

In addition to its focus on the four questions listed in its charge, the Subcommittee also noted that a group of common themes emerged from its deliberations and review that warranted comment and consideration. These themes included: the need for an improved, statistically valid, and rigorous sampling strategy; timeliness of reports and reporting; harmonization of data among the three components of the program; and the creation of a contemporary surveillance platform that would enable the participants to conduct hypothesis-driven research, make inferences from a stronger statistical foundation, and add greater value for data utilization and the conversion of data into information to better support policies, regulations, and public health impact.

Our responses and findings to the four questions, in large part, address these recurring themes. The Subcommittee noted that there continues to be financial constraints for the NARMS program. Yet, when considering the increasing value of NARMS and the very favorable upside potential to accrue more benefits in the future, the Subcommittee is impressed with the current return on investment and would rank NARMS as a high priority and mission-critical function, especially for the Center for Veterinary Medicine (CVM)/FDA. In addition, the Subcommittee believes that creating a business plan may also be helpful for planning purposes and encourages the participants to also explore funding possibilities outside of the traditional federal budget process.

NARMS is considered a public health system with an emphasis on protecting human health; yet, the animal health benefits seem underappreciated. It is important that all three partners of NARMS accrue benefits as true partners. Veterinarians and animal health officials are also clients and would not be well served if their antimicrobial therapies become less effective due to a building resistance problem no matter what the cause.

Practicing veterinarians and producers are likely to make better decisions regarding prudent and therapeutic drug use if they were more knowledgeable about the level of resistance/susceptibility of pathogens to antimicrobial agents. In order to elucidate the risk factors for animal and human infection by antimicrobial-resistant pathogens and understand the true impact of antibiotic use, non-use and resistance to human health, animal health, trade, and environment, better data sharing is essential.

Although not a question posed to the Subcommittee, there were a number of public comments that were critical of the fact that actual drug usage data were not readily accessible or shared. This reality creates a significant limiting factor to the further analysis of NARMS data. The Subcommittee recognizes that there are confidentiality issues of concern; however, the Subcommittee also believes that this data gap represents a critical barrier for NARMS to achieve its objectives and further utility. The group encourages the industry to work with NARMS and to try to develop a confidential component of NARMS data that better links such data with true public health impact, yet does not compromise sensitive industry data.

***Question 1*: Are there inherent biases in the sampling strategies employed in NARMS? If so, how can they be improved to ensure that the data and our interpretations are scientifically sound given current resources?**

NARMS, as originally conceived, used bacterial strains being collected for other purposes for screening for antimicrobial resistance. It can be argued that at the time the program was initiated that this was an appropriate approach, reflecting uncertainties about what would be found, and the potential utility of the data. In the intervening 10 years, the value of the data has become increasingly obvious, with NARMS findings playing a key role in both epidemiologic studies and regulatory activities. This was underscored in the public meeting, where there was virtual unanimity among representatives from industry, consumer groups, and academia as to the importance of the system. Under these circumstances, there is a need to critically re-evaluate the sampling approach to assure that the data being generated can withstand scrutiny from both a scientific and regulatory perspective. The Subcommittee strongly believes that resistance data must be able to withstand legal and regulatory scrutiny and challenges. This underscores the importance of a careful review of the potential biases, especially in USDA isolates. Failure to do this will likely limit the long-term value of the NARMS findings. While appropriate sampling may initially cost more than using a convenience sample, it invariably results in long term savings, because poorly collected data do not have to be discarded, and questions can be answered efficiently with appropriately sized samples.

NARMS currently screens strains from three sources for antimicrobial resistance:

1. Human Component: This component draws from isolates submitted to state health department laboratories for testing and species confirmation. Since 2003, all 50 states have been forwarding a representative sample of non-typhi Salmonella,

Salmonella typhi, and *Escherichia coli* (*E. coli)* O157:H7, and 10 states (in FoodNet) have been participating in FoodNet surveillance.

Potential biases: Samples are collected as a proportion of all isolates submitted to the participating state health department laboratories. However, there are clear differences from state to state with regard to which isolates are received by the state health department laboratories. In many states, clinical laboratories are not required to submit all isolates (or any isolates) of a particular species; and, consequently, there may be striking differences among states and among regions of a single state (i.e., urban vs. rural) in relative number and source of isolates. Biases may also arise at the physician level: stool cultures may not be ordered until after a patient has failed conservative therapy (including, in many instances, an empiric course of ciprofloxacin). Finally, it must be recognized that this is a passive system: With the exception of FoodNet states, there is no effort to assure that isolates, even those whose submission may be required by law, are actually submitted.

Ideally, one would like to see a true national random sample of clinical isolates in each species of interest with comparable representation from all states and all regions within states. If the current sampling scheme is maintained, there must be some type of data stratification to provide data that accurately reflect national trends. There is also a need for some type of periodic active sampling of clinical labs, to assess the representativeness of the isolates being submitted through NARMS to the overall population of clinical enteric isolates. Neither of these approaches will address the issue of potential biases at the physician level: Targeted studies will also be needed to assess the actual significance of this potential bias.

There is definite value in assessing overall levels of antibiotic resistance among isolates that are part of the intestinal flora of healthy human populations. As an example, documentation of high population-based levels of resistance to vancomycin among enterococci from healthy adults in Europe provided a key data point in decisions to ban further use of avoparcin in animals. In this context, it should also be recognized that there is great fluidity in gene movement among bacterial species; and, consequently, presence of resistance genes in any species is of potential interest in understanding emergence of resistance in humans. Continued surveillance in this area should be strongly encouraged as part of the NARMS mission. However, while some samples for these types of studies have been taken from normal human volunteers, most appear to have come from patients for whom stool samples were submitted for other reasons. It must be recognized that samples from this latter group have definite biases, given that these patients will have had other medical conditions that have prompted samples to be collected.

2. The Retail Meat Component was launched in 2002 with isolates from retail meat collected by investigators in selected FoodNet sites. The methodology for the sampling has undergone subsequent revision, but the overall sample size remains very small, particularly if any type of stratification is done on the data.

Potential Biases: Samples are collected from a limited number of areas for a small number of products. While major trends may be observed, the small sample size and lack of a national sampling strategy make interpretation of these data difficult.

These are extremely important data, as they reflect sampling at one of the closest points to the "fork" in the farm-to-fork continuum. A statistically valid national sampling scheme may not be possible given the potential cost. In this setting, serious consideration should be given to limiting sampling to specific, hypothesis-driven studies designed to provide an understanding of sources and risk factors for antimicrobial resistance.

3. Animal Component: This component utilizes isolates from three primary sources: (a) The USDA in-plant Hazardous Analysis and Critical Control Point (HACCP) monitoring system; (b) clinical isolates submitted through diagnostic laboratories; and (c) isolates collected as part of the USDA-Animal Plant Health Inspection Service (APHIS) National Animal Health Monitoring System (NAHMS).

Potential biases: The USDA in-plant HACCP monitoring does not reflect a random sample of processing plants, a problem exacerbated by the fact that plants that are out of compliance have increased numbers of samples collected. At a minimum, sampling must be restricted to the first set of samples collected in a plant (i.e., exclusion of additional sampling sets from plants that are not in compliance). USDA should be encouraged to assess its current HACCP sampling strategy and to see if modifications in the sampling strategy can be made to make the sample more closely resemble a truly representative national sample. Alternatively, consideration should be given to an ongoing "baseline" sampling scheme to provide nationally representative data on levels of contamination of raw product at the time of slaughter.

NAHMS data represent a statistical approach to sampling on-farm populations. While potentially useful, these samples fail to provide a true national sample of on-farm isolates. As with the retail food study, on-farm data are essential in understanding movement of resistance through the farm-to-fork continuum. However, given the difficulties in obtaining truly representative national data at an on-farm level, it may be best to limit on-farm isolate collection to specific, hypothesis-driven research studies designed to identify sources and risk factors for acquisition of resistance.

Clinical diagnostic laboratory data have potentially the greatest biases, representing a completely non-random sample and a sample that comes from settings in which there is likely to have been antimicrobial use. These data have potential value as an "early warning system" for emergence of resistance in the setting of clinical use of specific antibiotics. However, these data should not be used in epidemiologic studies and clearly should not be combined with animal data from the other isolate sources noted above. These samples also represent the only attempt to characterize resistance/susceptibility of targeted pathogens recovered from companion animal populations and exotic pets, a growing concern for veterinary medicine and public health research.

The Subcommittee noted with interest the progress of three USDA agencies – APHIS, the Agricultural Research Service (ARS), and the Food Safety and Inspection Service (FSIS) – in implementing the Collaboration in Animal Health and Food Safety Epidemiology (CAHFSE) program. This program is designed to be both a food animal disease monitoring system and a bacteria monitoring system taking place on-farm and in-plants over time. A particular emphasis of CAHFSE is to address issues related to antimicrobial resistance. This joint effort could eventually help improve the understanding of the process of antimicrobial resistance and the link from the farm-to-table continuum. Questions about the true burden of illness and an attempt to quantify public health impact with the emergence of resistance remain elusive at best. The Subcommittee is also concerned about the issue of confidentiality of on-farm data and the ability to link human and animal data sets. Yet, overall, there is real merit in the further coordination and linkage of data from all components in a timely manner; thus, the Subcommittee strongly encourages further pilots like CAHFSE to achieve greater specificity in our understanding and the discovery of new critical associations from the various sampling and epidemiological projects and studies.

FINDINGS:

- For human samples, there is an inherent bias, because clinical laboratories and physicians select and handle samples differently from state to state. While a true random sample would be ideal, it may not be completely feasible; thus, the Subcommittee believes that stratifications of the current sampling system would be useful and could assist in the identification of national trends. Furthermore, the adoption of a more active and targeted sampling strategy would also improve the current strategy.

- There is value in assessing the level of antimicrobial resistance present in the intestinal flora of healthy individuals. While NARMS attempts to do this, further bias may occur because of how these samples are selected. Thus sampling from a population of truly healthy individuals would be beneficial.

- With regard to retail meat, the relatively small sample size and lack of national sampling strategy limits a broader interpretation and inference of data. It may be more useful to adjust this sampling strategy to help answer specific, hypothesis-driven questions and studies.

- For the animal component, sampling biases occur because the current system does not reflect a randomized strategy for selecting processing plants. It would be useful for the USDA to redesign its HACCP sampling strategy to become a truly nationally representative strategy.

- The use of data from USDA's National Animal Health Monitoring System and other on-farm data has real potential utility but is currently limited because it is not representative of a national sample. Therefore, the NARMS sampling strategy

may prove more useful if implemented based on specific hypothesis-driven research where risk factors for resistance would be the focus.

- Clinical diagnostic laboratories data are especially biased and should be limited to use as an early warning system for emerging resistance.

Question 2: **Are there epidemiological and/or microbiological research studies that would better serve the goals of NARMS and the regulatory work of FDA?**

Applied research is already a cornerstone of all three components of NARMS. This research can be grouped into three broad types or categories: the development and optimization of laboratory methods for susceptibility testing, strain characterization, and resistance determinant detection; use of NARMS isolates and data as platforms to achieve program goals; and pilot studies to explore new program opportunities and approaches. Examples of the first type include development of a Clinical and Laboratory Standards Institute (CLSI)/ National Committee on Clinical Laboratory Standards (NCCLS) approved broth microdilution method for Campylobacter susceptibility testing and development/adaptation of genotyping methods (e.g., Pulsed Field Gel Electrophoresis, Multilocus sequence typing) for Salmonella and Campylobacter. Examples of completed or existing platform studies include epidemiological and microbiological studies into the clinical consequences of multiple drug resistant (MDR) pathogens and the dissemination of resistant bacteria and genes. Finally, examples of the third type include the USDA-funded CAHFSE program, Iowa Retail Meat, and VetNet projects.

An active applied research program is critically important to the continued success of NARMS, and the Subcommittee believes that it is appropriate to continue research in these three broad categories with expansion into a fourth, which is targeted hypothesis-driven research. The progress already made in methods development should be expanded with increased emphasis on detection of resistance genes in fecal, carcass, and food samples, without regard to the species of bacteria in which they reside or whether they are from pathogens or commensals. Development of molecular methods for routine identification of resistance genes from field samples is an important long-term goal for the program. The apparent ease with which many of these genetic determinants spread among bacteria and ecological niches indicates that there should be a fundamental expansion of emphasis on the unit of analysis in monitoring and research from the organism level exclusively to both the organism and gene levels. Pilot studies are valuable testing grounds for new methods, approaches, and sampling plans, but they should be carefully planned and coordinated to ensure efficient use of resources.

There is also a need for more hypothesis-driven research to provide answers to some important public health questions related to the NARMS mandate, including the assessment of human health risks. This research should expand the NARMS research portfolio; and, ideally, it would enhance collaboration with scientists in academia and other sectors and be facilitated, or, in some cases, made possible by leveraged funding from outside sources, such as NIH. This would also be facilitated by improvements in

data management, linkage, and retrieval. In particular, this research should improve our understanding of the ecology of antimicrobial resistance, the flow of resistance genes and bacteria through the farm-to-fork continuum, and the resultant impact on human health. This could be pursued in a variety of ways, for example, by identifying one or more well-defined locales or catchment areas where it is feasible to collect antimicrobial use and resistance data that can be directly linked epidemiologically. This extends the concept of the pilot study to a large epidemiological study. A potential deficiency of this type of research, however, is that given the practical limitations in current sampling and laboratory techniques, it has limited capacity to measure some of the longer-term implications of resistance selection pressures in microbial populations, such as the dissemination of resistance genes among microbial ecosystems or co-selection by linkage of genetic determinants that may take years to develop in disparate parts of the country or in various animal or human ecosystems. Therefore, there still is a need for hypothesis-driven research that identifies associations between antimicrobial use and resistance across broad populations and regions (e.g., antimicrobial use and resistance at the national level in both animals and humans).

FINDINGS:

- The Subcommittee strongly believes that the NARMS program should further develop its research portfolio in the areas of: laboratory methods; platform development and studies in support of program goals; and pilot projects that enhance NARMS goals, utility, and approach.

- In addition, the Subcommittee encourages the program to expand its hypothesis-driven research, especially with a new focus on assessing human health risks. To do this effectively, the Subcommittee further encourages the NARMS Team to expand its research collaboration and partnerships in academia and with the NIH.

- The ecology of resistance is complex and dynamic, and hypothesis-driven research represents the next logical area of expansion. Understanding the flow of resistance genes and bacteria across the farm-to-fork continuum and the resultant human health impact is key to future prevention and intervention strategies, and, thus, a critical research focus for the NARMS program.

***Question 3*: Are our current plans for data harmonization and reporting appropriate? If not, what alternative approaches would you consider, and what should be the top priorities for harmonization and reporting?**

It is clear from all parties involved in NARMS, as well as public commentators, that there is a crucial need for a real-time integrated database that would allow access to all the components of the NARMS program (CVM, USDA [including FSIS, APHIS, ARS], and CDC) and the production of timely reports. Given the nature of microbiological data, as well as rapidly changing and emerging problems, timeliness to data access is essential. Great progress has been made in harmonizing microbiological techniques; the focus now must be on creating an easily accessible and searchable database.

To accomplish this, it is important that the participants define the attributes of a single database structure that would allow all data from all three NARMS components to be tabulated in a single database. The structure should be related to how data will be interpreted. All components should agree on data needs and linkages, as well as what is actually desired from the data. Considerations should be given to how the data will be used; that is, will they be for surveillance, monitoring, research, or regulatory use, and understanding any bias inherent in any of the sampling strategies. These attributes should then define the appropriate database architecture. This structure must be defined from the perspective of the data attributes and not the information technology resources needed to implement it.

This database should be a searchable and dynamic tool and not a series of flat portable document format (PDF) files. The Subcommittee foresees that this database would be populated real-time using modern web-based strategies with off-the-shelf software. For all three units, once data have been collected and validated according to local agency standards, the data should be routinely entered into the database. If all data elements are not available (e.g., pulse-field gel electrophoresis results), they can be entered as the data are generated. Milestones using tools such as Gantt charts should be defined to streamline data capture and timely entry into the database.

The various NARMS units can design their own software interfaces to access this central database depending on their individual needs for data analysis and available software support. This would still allow individual NARMS components to perform their own level of data analysis and summarization. Because of the confidential nature of some of these data, the integrated database should first be restricted to internal government use. This is a priority for both public health and regulatory needs. Should public access be desired in the future, a segregated database could be constructed where confidential data elements are restricted to government access and public data is released separately as data are generated.

The advantage of such a real-time integrated database is that report generation could also be real-time. The existing delay in producing executive reports would be significantly reduced. Report format would be a function of the unit's needs for analysis and not a function of database structure. A range of types of reports would be possible as no one product will fit all needs. Simple tabular presentations as presently produced may not be adequate for some groups/stakeholders. Such a tool would also facilitate the writing of scientific publications as well as mitigating outbreak characterizations. Rapid querying by NARMS personnel would be available as close as their desktop computers. Today's database technology is sufficiently portable and secure that the unique software/hardware environments exist so that each NARMS participant should be able to easily access a central database. This database should be maintained at a single site to ensure database and data security, and plans for maintenance should be built into the system. The sophistication of the database structure is not crucial; the uniform data structure capable of categorizing all three datasets is crucial. These data must be cross-linked by species, product, and microbiological descriptors, as well as data elements needed for proper interpretation.

The concept of database integration could also be carried a step further by attempting to start the collection of drug use data. One source is data that are mandated by existing regulations should be reported by manufacturers on gross drug sales. However, these data are not granular enough to correlate to the species or local farm level. In an ideal world where financial resources or bureaucratic divisions are not constrained, microbial data collection would be accompanied by metrics of drug exposure. Techniques such as existing multi-antimicrobial drug screening approaches used by FSIS and FDA for residue monitoring might be applied to select tissue samples collected for microbiology to confirm drug exposure. A pilot study could be employed to assess the feasibility of this approach.

Finally, the lag time between data collection and report generation is excessive and diminishes the utility of information. In summary, there is no excuse for the present situation where report generation lags some four years behind data collection. Data should be entered on a real-time basis. Public health and regulatory decision making requires real-time data. The Subcommittee envisions this process to start with internal government data sharing and then move to public data access of non-confidential elements. Should hard-copy reports still de desired by specific shareholders, such a system would facilitate both detailed analysis as well as timely publication.

FINDINGS:

- There is a critical need to create a real-time integrated database for all components of the NARMS program and the production of more timely reports.

- The use of the data and the data attributes should dictate the information technology solution. A web-based, real-time system is envisioned that would be flexible enough to allow separate data-entering, reporting, and handling potentially confidential data.

- The Subcommittee understands the need for accurate and responsive data that support improved decision making and regulatory analyses. However, the NARMS Team is encouraged to move toward a database that can be more readily shared with researchers and other users who could add further value to the data and conduct research or for further analyses. The Subcommittee further stressed the need to capture drug use and/or exposure data as part of this database.

- By improving the speed and quality of reports, the Subcommittee believes that the NARMS Team could then expand the utility of the information to include: pre-market approval planning; better linking of animal and public health communications; and expansion of utility and availability – both to other researchers who could add further value and utility for the NARMS program and eventually directly to the public.

***Question 4*: Are the current NARMS international activities adequate to maintain a significant collaboration with worldwide efforts to mitigate the spread of antimicrobial-resistant food-borne bacteria?**

International activities are critical, because antibiotic resistance is very much a global problem. Today, approximately15% of our food is imported with the likelihood that food imports will substantially grow, and these products will largely be coming from developing countries. Many imported foodstuffs, such as seafood and fresh fruits, are already imported in much higher percentages. Because of the rapidly expanding global food system, the Subcommittee envisions that increasing levels of collaboration must occur among countries and international health organizations worldwide.

As a global issue, antimicrobial resistance cannot be addressed by a single country's program. The complexity of the food system and global distribution of foods demonstrate the need for continued collaboration with other international antimicrobial resistance monitoring programs. It is also crucial that at the international level there is a single and unified consensus representing all the NARMS partners. There should be no confusion or differences in the interpretation of NARMS data.

In 2003, a NARMS report (NARMS-Enteric Bacteria 2003 Executive Report) recognized the potential health hazards of antimicrobial resistance. The World Health Organization (WHO), the Food and Agriculture Organization (FAO) of the United Nations, and the World Organisation for Animal Health (aka OIE) recommended that countries implement national monitoring programs for the use of antimicrobials in animals and the occurrence of antimicrobial resistance in bacteria from animals, foods of animal origin, and cases of human illness. Challenges have not changed with regard to usage of antimicrobials and the occurrence of resistance. The Subcommittee believes that there is a need to compare the usage of antimicrobials and the occurrence of resistance among countries; to integrate our knowledge of pathogens and trends; to identify targeted research themes; to continue the development of risk assessment models; and to continue the development of policies for containment.

Currently, all three "arms" of the NARMS program have international activities; yet, better coordination among the agencies should be an important goal. There seems to be no question that this is an important element of all three "arms," yet synergies among the separate programs must be reinforced.

The CVM has a multi-pronged approach that includes education/outreach, expanded participation in international activities, and increased research and surveillance programs. Although Pulse-Net, predominantly a CDC project, continues to expand globally, it requires further expansion done even more rapidly.

NARMS currently supports the efforts of various international organizations (e.g., Danish Integrated Antimicrobial Resistance Monitoring and Research Programme; Canadian Integrated Program for Antimicrobial Resistance Surveillance; ResistVet Project: The US-Mexico-Guatemala Antimicrobial Resistance Monitoring Program for Foodborne

Pathogens; and Global Salm-Surv (GSS)). NARMS and GSS have played an important confirmatory role with regard to antimicrobial resistance in the U.S. and other countries. This program should be provided continuing support and must be improved to include better surveillance. The Subcommittee encourages the continued cooperation and support of the WHO GSS through Institute Pasteur, the Danish Institute for Food and Veterinary Research, CDC, the Canadian Public Health Agency, CVM, the Animal Science Group of the Netherlands, OZ FoodNet Australia, and Enter-Net. Furthermore, ResistVet, a project between the U.S. and Mexico, should be nurtured and encouraged – eventually leading to an independent monitoring program in Mexico.

It is time for international partners that collaborate in surveillance programs to develop stronger and more robust programs for monitoring public health issues within participating countries. WHO has endorsed a tripartite approach to include isolates from human clinical cases, food animal and retail meats, and superficially conducting antimicrobial resistance and monitoring food-borne pathogens. Such an approach should continue to be endorsed by the NARMS Consortium.

Scientist training, particularly microbiologists involved in international antibiotic resistant programs, should be encouraged and supported. Continuing education and training are essential for the creation and implementation of quality programs. International workshops devoted to embracing the quality of data collection and uniform reports pertaining to surveillance are growing in importance.

Globalized trade has accentuated the importance of international cooperation in training, surveillance, and in monitoring and controlling microbial outbreaks. Such globalization has also brought about the importance of recognizing emerging zoonotic diseases – again a need for international cooperation and communication. As a result of this globalization, a number of important international collaborations have evolved, including the International Network of Integrated Surveillance for Antimicrobial Resistance in Enteric Bacteria (INISAR). It is imperative, particularly in a global economy and one in which the U.S. is a major stakeholder, that international ties and collaboration should continue and be strengthened.

FINDINGS:

- Antimicrobial resistance is a global issue and cannot be completely understood or addressed by individual national programs; thus, the current NARMS international activities must be continued and expanded, especially as imported food supplies to the U.S. are increased.

- There is a further need to improve coordination among international animal and human health organizations with regard to antimicrobial resistance. The work of the NARMS Team, along with a handful of similar global activities, should help provide an international leadership forum and serve as both a critical mass to expand activities and a model for other countries and organizations to emulate.

- Internationally, NARMS or NARMS-like programs must recognize the continuing need to adopt advanced technologies, the importance of quality data collection, and timely reporting in recognition of emerging public health issues.

- The Subcommittee endorses the idea that there should be a single U.S. NARMS position, a single entity or spokesperson to represent NARMS in global settings, and a standardization of messaging and reporting.

- The NARMS Team currently assists in international training, and the Subcommittee encourages the continuation and expansion of this important role.

Summary

The NARMS subcommittee was impressed with the genuine commitment and dedication of the NARMS participants and with the collegial and constructive presentations and remarks from the public. The NARMS program has made outstanding progress over the last decade and has gained the respect and acceptance of a diverse public, including pharmaceutical companies. The evolution and maturation of NARMS since its inception in 1996 has been steady and has been characterized by continuous learning and improvement. There are clearly a number of existing activities that are going well and deserve to be continued. Yet, the Subcommittee also found several critical areas of need that were disclosed in its evaluation of the four questions posed to the group and have been listed in the Subcommittee findings. The Subcommittee believes that the NARMS participants are now in a better position to build on the current good will and program strengths that may not have existed in the past. Therefore, the NARMS Team should not just consider how the program can continue to meet its current objectives but should now consider and explore new opportunities not envisioned a decade ago.

There is nothing on the horizon to suggest that the progressive complexity and interdependence of animal agriculture, global food systems, and public health will change or slow down. On the contrary, these integrated systems continue to expand in scope, scale, and potential consequences. Therefore, in addition to responding to specific findings, the Subcommittee encourages the NARMS Team to step back from just considering incremental changes and improvements and to now reconsider the program's current objectives in light of the extraordinary and unprecedented changes in agriculture, industry, foods, and the contemporary challenges to public health. The Subcommittee believes that NARMS data should become more predictive, responsive, and expansive, including the addition of pre-market product approval, global and better linked through wider stakeholder involvement to animal and public health communities.

The Subcommittee encourages the development of a 10-year NARMS plan and consideration of beginning a new phase of program development. It is a propitious time for the NARMS Team to implement a visioning process, develop a concurrent business plan, and create an expanded opportunity horizon to improve public and animal health in this new era. The NARMS program has performed well when one considers its genesis, convenience-sampling strategy, limited resources, and relatively differing agency cultures. However, these legacy and founding principles no longer fit the growing importance of the program or the growing societal and public health need.

Acknowledgements

The Subcommittee expresses its appreciation to the members of the NARMS Team who made presentations; to public presenters and those submitting comments; and to FDA staff, including Dr. Carlos Peña and Ms. Joanne Kla, who capably supported the planning and logistics for the Subcommittee meeting. These collective efforts were invaluable to our Subcommittee and to the completion of this report.

Appendix 1: Subcommittee Members and Participants

Larry M. Granger, DVM, is currently the Director of the Centers for Epidemiology and Animal Health (CEAH), part of the United States Department of Agriculture's Animal and Plant Health Inspection Service, Veterinary Services. Dr. Granger earned his degree in Veterinary Medicine in 1979 from Michigan State University. He was in private practice for nine years before joining the Michigan Department of Agriculture as the Pseudorabies Eradication Program Manager. He stayed with the Michigan Department of Agriculture and held several different positions before becoming Veterinary Services' Associate Deputy Administrator for Emergency Management in 2003, a position he held until he became the Director of CEAH, in 2006.

Susan K. Harlander, PhD, Senior Vice President Government and Industry Relations, BT Safety LLC. Dr. Harlander has more than 20 years experience in the food industry, with nine of those years in senior research and development management positions where she was involved in several trace recall incidents involving dairy and processed food products. She has served on numerous dairy and food industry trade association committees, including the Grocery Manufacturers of America, National Food Processors Association, and the International Dairy Foods Association to name a few. Dr. Harlander serves as a consultant to farm organizations, grain processors, food manufacturing companies, trade associations, and biotechnology providers, and has been active in domestic and international issues related to traceability and identity preservation of genetically modified foods. While an Associate Professor in the Department of Food Science and Nutrition at the University of Minnesota, Dr. Harlander served on numerous Scientific Advisory Boards for food companies and spent summers working for companies like General Mills and Procor Technologies. She was the principal investigator on numerous grants and has published over 110 referred papers, book chapters, and monographs and has made over 400 presentations to scientific and lay audiences. She has served on FDA's Science Board; FDA's Food Advisory Committee; USDA's National Agricultural Research, Education, Extension and Economics Advisory Board; and the NRC's Board on Agriculture and Food Chemicals Codex Committees. As a former Associate Professor of Food Microbiology and Biotechnology, Dr. Harlander brings extensive experience in food microbiology and an understanding of biological and chemical agents that could be used in food bioterrorism, as well as naturally occurring pathogens that contaminate the food supply.

Lonnie King, DVM, Director, National Center for Zoonotic, Vector-Borne, and Enteric Diseases, CDC, received his Bachelor of Science and Doctor of Veterinary Medicine degrees from The Ohio State University in 1966 and 1970, respectively. He earned his Master of Science degree in epidemiology from the University of Minnesota while on special assignment with the U.S. Department of Agriculture in 1980. He also received his Master's degree in public administration from American University in Washington, DC, in 1991. Dr. King is a board-certified member of the American College of Veterinary Preventive Medicine and has completed the Senior Executive Fellowship Program at Harvard University. He has served as president of the Association of American

Veterinary Medical Colleges from 1999-2000 and was vice chair for the National Commission on Veterinary Economic Issues from 2000-2004. Dr. King also has served as administrator for the Animal and Plant Health Inspection Service, U.S. Department of Agriculture. He recently completed his tenth year as dean of the College of Veterinary Medicine, Michigan State University, and has assumed the position of Director of the National Center for Zoonotic, Vector-Borne, and Enteric Diseases at the Centers for Disease Control and Prevention in Atlanta. Dr. King is a member of the National Academies of Science through his election into the Institute of Medicine, is on the Scientific Advisory Board for the FDA, and is a member of the newly formed Pew Commission Studying Animal Agriculture and Public Health.

Scott A. McEwen DVM DVSc, Diplomate ACVP, is a Professor, Department of Population Medicine, University of Guelph, Guelph, Ontario, Canada. Dr. McEwen obtained his DVM and Doctor of Veterinary Science degrees from the University of Guelph. His research focuses on the epidemiology of foodborne infections in food animal populations, particularly *E. coli* and antibiotic resistant organisms, but also Salmonella and other pathogens. He has extensive experience in conducting epidemiological studies in cattle, swine, and other food animal species and has also participated in a number of studies of zoonotic infections in humans, including *E. coli* O157:H7 and antimicrobial resistance in commensals. His research on *E. coli* O157:H7 and related organisms focuses on the distribution of fecal shedding in cattle and risk factors for infection in cattle and humans. He and his co-workers are also active in simulation modeling of potential intervention strategies (including vaccination) for this infection on farm and throughout the food chain. His research program in antimicrobial resistance focuses on the determinants of selection and assessment of human health risks.

Since 1986 he has taught food safety to veterinary students and graduate students in a variety of degree programs and has been the principal research advisor of over 25 MSc and PhD students. He is author or co-author of over 100 publications in referred scientific journals and has delivered invited research presentations in nine countries.

He consults on food safety, antibiotic resistance, epidemiology, and other veterinary public health matters with a number of governmental and non-governmental organizations in North America and Europe, notably various food animal industry groups, the Alliance for the Prudent Use of Antibiotics, the World Health Organization, the United States Food and Drug Administration, and Health Canada.

He recently chaired Health Canada's Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health, the World Health Organization's evaluation of the termination of the use of antimicrobial growth promoters in Denmark, the FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment, and an Expert Advisory Panel to a Judicial Review of Meat Inspection in Ontario.

J. Glenn Morris, Jr., MD, MPH&TM is Professor and Chairman of the Department of Epidemiology and Preventive Medicine at the University of Maryland School of Medicine and interim Dean of the University of Maryland, Baltimore, School of Public Health. He received his MD degree and a master's degree in public health and tropical medicine from Tulane University, New Orleans. He served as an Epidemic Intelligence Service Officer in the Division of Enteric Diseases at the then Centers for Disease Control in Atlanta from 1979-81. He is board-certified in both internal medicine and infectious diseases. Dr. Morris has authored over 60 textbook chapters and symposium proceedings and over 170 articles in peer-reviewed journals. He has had continuous federal grant funding since 1984; his scholarly contributions were recognized by election to the American Society for Clinical Investigation in 1996. He has served on four National Academy of Sciences expert committees dealing with food safety. From 1994-1996, he worked with the Food Safety Inspection Service, U.S. Department of Agriculture, on the preparation of the Pathogen Reduction/HACCP regulations. In 2005, he was awarded the James D. Bruce Memorial Award for Distinguished Contributions in Preventive Medicine by the American College of Physicians. Dr. Morris continues to have a strong research interest in the area of emerging pathogens: he maintains an active, NIH-funded laboratory working in the area of molecular genetics and molecular epidemiology; is involved in hospital studies looking at emergence of resistant microorganisms; has worked extensively with clinical, laboratory, and environmental issues related to harmful algal blooms; and serves as co-PI of the CDC Emerging Infections Program sentinel surveillance site (FoodNet) in Maryland.

Jim E. Riviere, DVM, PhD, is the Burroughs Wellcome Fund Distinguished Professor of Pharmacology; Director, Center for Chemical Toxicology Research and Pharmacokinetics, College of Veterinary Medicine; and Director of the Biomathematics Program of the College of Physical and Mathematical Sciences, North Carolina State University (NCSU), in Raleigh, NC. He is an elected member of the Institute of Medicine of the National Academies, serves on its Food and Nutrition Board, and is a fellow of the Academy of Toxicological Sciences. Dr. Riviere received his BS (*summa cum laude*) and MS degrees from Boston College and his DVM and PhD in pharmacology from Purdue University. He is a member of Phi Beta Kappa, Phi Zeta, and Sigma Xi, and has served on the Science Board of the Food and Drug Administration. His honors include the 1999 O. Max Gardner Award from the Consolidated University of North Carolina, the 1991 Ebert Prize from the American Pharmaceutical Association, the Harvey W. Wiley Medal and FDA Commissioner's Special Citation, and the Lifetime Achievement Award from the European Association of Veterinary Pharmacology and Toxicology. He is the Editor of the Journal of Veterinary Pharmacology and Therapeutics and co-founder and co-director of the USDA Food Animal Residue Avoidance Databank (FARAD) program. He has served as an officer in various Specialty Sections of the Society of Toxicology, and has served on the Editorial Boards of various toxicology, pharmacology and veterinary journals. He has published over 400 full-length research papers and chapters, holds five U.S. Patents, and has authored/edited 10 books in pharmacokinetics, toxicology, and food safety. His current research interests relate to applying biomathematics to problems in toxicology, including the risk assessment of chemical mixtures, pharmacokinetics,

absorption of drugs and chemicals across skin, and the food safety and pharmacokinetics of tissue residues in food producing animals.

John A. Thomas, PhD, was born and educated in the Midwest. He received his undergraduate degree at the University of Wisconsin and his MA and PhD degrees at the University of Iowa. He has held professorships in departments of pharmacology and toxicology in several medical schools including Iowa, Virginia, and West Virginia. Professor Thomas has been the mentor for many doctoral students and has trained several postdoctorals. From 1973 to 1982 he served as Associate Dean of the School of Medicine at West Virginia University where his responsibilities included graduate programs and research. In 1982, Dr. Thomas moved into the healthcare industry where he became Vice President for Corporate Research at Baxter Healthcare. While in industry, he was involved in new drug development, including recombinant DNA-derived therapeutic agents. Dr. Thomas served as Vice President at the University of Texas Health Science Center at San Antonio from 1988-1998. He is the author of more than a dozen textbooks and research monographs and has published nearly 400 scientific articles in the area of endocrine pharmacology and reproductive toxicology. He is a member of numerous societies, including the Endocrine Society, the Teratology Society, American Society for Pharmacology and Experimental Therapeutics, Society of Toxicology, and the American College of Toxicology. Professor Thomas serves on several editorial boards of biomedical journals and has been a member of the National Library of Medicine Literature Selection Technical Review Committee. Dr. Thomas served as a Specialty Editor for Toxicology and Applied Pharmacology and is on the Editorial Board of Food and Chemical Toxicology. He served as member on the Air Force Science Advisory Board. He has been a member of the Institute of Medicine/National Academy of Science Committee on Micronutrients, and he is past-Chairman of the Expert Advisory Committee of the Canadian Network of Toxicology Centers. He is a member of the FDA Science Advisory Board. Recently, Dr. Thomas served as Chairman of the NTP/NIEHS, Center for Evaluation of Risk to Human Reproduction, Expert Panel on Ethylene and Propylene Glycol as well as being a member of the Expert Panel on soy infant formula and genistein. He is a Diplomate and Fellow in the Academy of Toxicological Sciences as well as a Fellow in the American College of Toxicology. He continues to serve on many scientific boards and committees in the chemical and pharmaceutical industry. He served as Vice President for the Texas Society for Biomedical Research, as a member of the Board of Trustees of the International Life Sciences Institute and on the Board of Directors of the Academy of Toxicological Sciences. Dr. Thomas is Past-President of the Academy of Toxicological Sciences. He was named the 1999 recipient of the Distinguished Service Award from the American College of Toxicology. Dr. Thomas is Past-President of the American College of Toxicology. He is the recipient of several national awards, including the Merit Award from the Society of Toxicology, Certificate of Scientific Service (U.S.E.P.A.), Distinguished Lecturer in Medical Sciences (A.M.A.), Distinguished Service Award from the Texas Society for Biomedical Research and holds Distinguished Alumni Awards from both the University of Wisconsin and the University of Iowa. Recently, he was awarded an FDA Commissioner's Special Citation. He is an elected foreign member and Fellow of the Russian Academy of Medical Sciences.

Appendix 2: NARMS Presenters from Federal Agencies

Tom Chiller, MD, MPH, Past Chief of NARMS; Mycotic Diseases Branch; Division of Foodborne, Bacterial, and Mycotic Diseases; National Center for Zoonotic, Vector-Borne, and Enteric Diseases, CDC

Paula J. Fedorka Cray, PhD, Antimicrobial Resistance Research Unit, USDA

Patrick F. McDermott, PhD, NARMS Retail Meats, Center for Veterinary Medicine, FDA

David G. White, PhD, NARMS, Center for Veterinary Medicine, FDA

Appendix 3: Public Presenters

Richard A. Carnevale, VMD, Animal Health Institute

Michael Feldgarden, PhD, Alliance for the Prudent Use of Antibiotics

Steven Larsen, PhD, National Pork Board

Steven Roach, Food Animal Concerns Trust

Hua Wang, PhD, The Ohio State University