

Richard A. Carnevale, VMD
Vice President, Regulatory, Scientific & International Affairs

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Centers for Disease Control and Prevention
National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion
Office of Antimicrobial Resistance
Attn: Antimicrobial Resistance Action Plan
Docket No. CDC-2011-0002
1600 Clifton Rd., NE., Mailstop A-07
Atlanta, Georgia 30333

**Re: Docket No. CDC-2011-0002; Draft Action Plan—A Public Health Action Plan
To Combat Antimicrobial Resistance**

The Animal Health Institute (AHI) submits these comments to CDC-2011-0002; Draft Action Plan—A Public Health Action Plan To Combat Antimicrobial Resistance. AHI is the national trade association representing manufacturers of animal health products – the pharmaceuticals, vaccines and feed additives used in modern food production, and the medicines that keep livestock and pets healthy.

General Action Plan Comments:

AHI believes that the Action Plan can be improved and offers its views for consideration in the next iteration of the document. The four main Focus Areas capture the essence of the activities needed; however, there is no apparent cross-linkage between them. To improve the strategic approach, it is necessary to demonstrate how the specific objectives on related topics in each Focus Area are connected and support each other. For example, *C. difficile* is mentioned in several Focus Areas, but it is not apparent how all of the objectives connect to one another. Similarly, food borne microorganisms and animal antimicrobials are mentioned in the Focus Areas, but there is no way to determine whether they are single activities or linked together in an overarching manner. AHI encourages the Co-Chairs to integrate across Focus Areas, those objectives that may be related or connected to each other in a separate section of the document.

AHI believes that it is important to state what the expected outcome of each objective will be. A metric that provides the current state or baseline is needed as well as the expected change that is anticipated as a result of the investment of resources for the objective. Using the prior Action Plan as a guide, the Co-Chairs are encouraged to extract specific accomplishments that resulted from implementation of specific recommendations. This may offer insight into the expectations for the next iteration of the Action Plan.

AHI notes that the Action Plan appears to be outdated in many sections. For example, stakeholder input from 2007 is mentioned; however, there is no mention of any more recent input, except by the government drafting group. A key topic area that illustrates this point is the FDA Science Board review of NARMS in 2007 and where a Strategic Plan to address those recommendations is now open for comment. As well, several objectives have projected completion dates in 2010, which suggests that the document remains in need of updating to incorporate realistic, not historical, target dates. Objective 3.7 is one area where this is most evident.

AHI notes that several original Action Plan recommendations have disappeared, with no explanation provided as to why. For example, the risk-benefit assessment of antibiotics used in food animal production has disappeared, yet is a valuable tool that should be employed. AHI suggests that the Co-Chairs justify the deletion of prior Action Plan objectives, perhaps in an Appendix, to provide transparency in the rationale to all stakeholders.

AHI notes that organizations such as WHO, OIE and Codex, which have elaborated guidelines to manage antimicrobial resistance in food animals and food borne antimicrobial resistant microorganisms have not been cited. Thus, it appears that the US Action Plan could be strengthened by stating the alignment with key principles from those organizations' documents. AHI suggests that the Co-Chairs state which objectives are consistent with international recommendations and which are unique to the US.

Specific Comments:

Page 1 - Executive Summary – 3rd paragraph

The meeting in 2007 is now 4 years out of date; inputs and updates since that time have not been discussed or agreed by the invitees – the updates in the current document were made by the government agencies who drafted the document. Thus, the stakeholder input which was received, and is stated to be “vital”, is diminished because of the length of time taken to issue this draft for comment.

Page 1 and 2 – Goals

These are very general, no timeline is provided, no prioritization is established, and no assessment of prior actions was made as to whether they were “successful” or not. There is a need for integration between goals, as appropriate to ensure coordination within an overarching strategy otherwise they are individual actions that are stand-alone.

Page 4 – Introduction and Overview - 3rd paragraph

AHI is pleased to note that the document reinforces the indications for antibiotic use in food animals. Herd and flock medication is essential to prevent disease before it spreads with the group. Since the implementation of FDA/CVM Guidance 152 in 2003, an outcome from the original Action Plan, the CVM has reviewed numerous products to ensure human microbial food safety prior to approval. Additionally, several peer-reviewed publications have estimated a

negligible risk to human health. The US FDA and USDA led the US Codex delegation that drafted the **Draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance** (<http://www.codexalimentarius.net/web/archives.jsp?lang=en>). Thus the assertion made in the last sentence of the paragraph that determining impact on human infections is an “ongoing challenge” is inconsistent with the actual situation where appropriate means are available. Moreover, since there is no longer a recommendation in the current Action Plan to conduct a risk-benefit assessment to address the matter, the Co-Chairs need to justify why they have chosen to not address the “ongoing challenge”. This paragraph should be revised to accurately reflect the current status of antimicrobial use in animals as it relates to public health and food safety.

Page 8 – IV. Product Development

AHI suggests that initiatives to foster antimicrobial development and innovation within FDA CVM are ongoing, such as Guidance 152, draft Guidance 209, and iVET, a partnership to address regulatory approaches for new technologies.

The Focus Areas

Page 10 - Focus Area I : Surveillance

AHI questions why the Action Plan only concentrates on “resistance” when susceptible pathogens also cause disease? Until susceptibility testing is completed, no one really knows if a pathogen is susceptible or resistant. Isn’t a more desirable goal to prevent infections or improve the outcomes for all pathogens? Indeed, in Objective 3.6 and 3.7, as well as in objectives that mention vaccines, the goal is to prevent infection, irrespective of whether the pathogen is resistant or not.

Goal 1: Improve the detection, monitoring, and characterization of drug-resistant infections in humans and animals.

What are the goals specifically...the word “improve” is not descriptive enough. Deficiencies in the current programs should be noted, so that transparency of approach is available.

- 1.1 b), c), d) – The Strategic Plan for NARMS, based on the FDA Science Board Review, is currently open for public comment. As such, it is premature to propose the specific recommendations because the program needs to be completely revised to provide for a purpose-specific, statistically-designed, representative sampling process, rather than to continue to operate in its’ current manner. AHI has provided comments to the NARMS docket (attached).
- 1.2 g) – AHI notes that in Objective 1.2, letter g) is out of sequence on the bottom of page 11; which begs the question as to whether other objectives were inadvertently excluded, or is this a simple typographical matter? The proposal for a representative bacterial isolate collection system – how can this be linked to any of the other isolate collection programs mentioned elsewhere, e.g. NARMS, etc.? AHI notes that the Co-Chairs support the

concept of an appropriately designed sampling system in this objective, in contrast to 1.1 b), c), d) objectives; as previously mentioned. What specifically is envisioned in terms of working with CLSI? This needs additional clarification. Does this objective include veterinary pathogens and animal isolates, as in Objective 10.3? This is another example of how the format of the document needs to be integrated to allow same-topic objectives to be linked together.

- 1.2 h) – What is the role of NARMS for foodborne isolates of salmonella, MRSA or *C. difficile* in this objective? AHI notes the Coordinator agency is CDC...why are not others also involved?
- 1.3 a), b), c), d) – It appears this objective is directed to looking for non-hospital-origin *C. difficile*, MRSA, and VRE, which from all indications in the literature is low to non-existent in food animal production settings. CDC has stated that MRSA is not a food borne pathogen; VRE are not found in US livestock or poultry since glycopeptides have never been used in these animals; and *C. difficile*, while found on some retail meats, has not been conclusively linked to resistance issues due to on-farm antibiotic use. Thus, resources allocated to this objective seem disproportionate to the need to know more about the risk for hospital infections from these bacteria.
- 1.5 f) – This objective would have a better placement in Objective 1.1 to link all NARMS activities together. The public NARMS meeting was held in July, 2010, so why is it on the list? Apparently there are no plans to hold future meetings since there is no mention of such possibilities.
- 1.6 c), d), e) – What is the role of CLSI documents and resources?
- 1.7 b) – What are “select” veterinary pathogens? Why use veterinary diagnostic lab isolates, which are “worst of the worst” and may represent treatment failures, instead of on-farm pre-treatment isolates? CLSI methods do not include all animal pathogens or have breakpoints for all antibiotics. Storage and public access to these isolates for product development need to be clarified. What linkage is there to Objective 1.2 g) and 10.3? Again, the Co-Chairs need to better integrate related objectives to ensure appropriate use of limited resources and successful outcomes.
- 1.8 b) – AHI has provided comments to the NARMS Strategic Plan (see attachment). Until the NARMS program is re-designed to provide useful information for on-farm, carcass, meat and human isolates, it seems premature for NARMS scientists to provide expert advice on an international basis. Instead, it may be more instructive for U.S. NARMS participants to obtain key learning from resistance monitoring programs in other countries that could be used to re-design the US program.
- 1.10 This Objective is unclear and seems to be supporting a pre-existing program. Since food borne pathogens and the environment are mentioned, it would seem appropriate for USDA to be involved.

Goal 2: Better define, characterize, and measure the impact of antimicrobial use in humans and animals in the United States.

The Co-Chairs need to clarify the general goal by providing specific metrics to be accomplished and what outcome is foreseen if the recommendations are enacted.

- 2.1 Sources of antimicrobial use have already been identified. AHI, NARMS, and FDA Section 105 have all provided sales data or estimates of use in animals. Developing a standard for a collecting and reporting scheme such as a DDD seems completely unworkable given the size of U.S animal production, the way animal drugs are currently distributed and used, and available resources. Furthermore, what would be the value of having such information on a national basis? The issues associated with the collection of antimicrobial use data has been previously thoroughly reviewed (*Special Issue: Antimicrobial Use Surveillance in Animal Agriculture*, Preventive Veterinary Medicine 73 (2006) 321–322) and Preventive Veterinary Medicine 73 (2006) 105–109.
- 2.1 a) – The approach seems to ignore how to protect proprietary data. There is also the question how to obtain use data vs. sales data. These are two separate types of data. Contextual data is also needed to help put such data into perspective. In other words, has there been an outbreak of a particular disease that resulted in increased sales, or a decrease in animal inventory due to depressed prices that affected antibiotic use and sales.
- 2.1 b) – What is a national antibiotic use point-prevalence survey?
- 2.1 d) – The objective is ongoing and has been published for 2010. The question of what to do with this sales data remains to be addressed.
- 2.1 e) – It seems these reports are already done, so why are they listed? What was the conclusion from the completed reports that met Goal 2?
- 2.2 It is not specified what existing data on correlations is available that can be collated for modeling purposes nor what will be modeled. AHI questions whether data in veterinary institutions is available for cephalosporin use and prevalence of VRE and macrolide resistance in pneumococci (which is not associated with an animal origin).

Page 18 – Focus Area II: Prevention and Control

What are the metrics for success? What success has been achieved from the 2001 plan for this Focus Area?

Goal 3. Develop, implement, and evaluate strategies to prevent the emergence, transmission, and persistence of drug-resistant microorganisms.

- 3.5 There are many Responsible Use guidelines available for animals, generated by the American Veterinary Medical Association in conjunction with the FDA/CVM, and others developed by professional organizations for particular animals (e.g. National Pork

Producers, National Cattlemen's Beef Association, etc.). Additionally, there are guidelines available from WHO, OIE and Codex that provide guidance to a variety of stakeholders. Thus, it is curious that the title of the section implies that there are no such "best practices" guidelines available. The Co-Chairs should revise this section to reflect that additional coordination and updating among these guidelines might be beneficial.

- 3.5 a) – The Co-Chairs need to provide justification as to why dairy production and antimicrobial resistant salmonella are listed as a specific objective. Apparently antimicrobial susceptible salmonella are acceptable and excluded from interventions, which is contrary to the food safety objectives in 3.6 and 3.7.
- 3.5 b) – AHI notes that this is the only recommendation with a specific funding amount listed – why? There is no clarity as to exactly what the awardees will "identify" or how the outcomes will relate to any other Action Plan goals or objectives. Since the date of June 2010 is now past, why is this included as a recommendation?
- 3.5 c) – AHI views this objective as redundant with 4.2 b) which covers FDA/CVM draft Guidance 209. As well, see the comment on Objective 3.5 above regarding Responsible Use guidelines.
- 3.6 This section deals with antibacterial products that are not specific for AMR in a) and b) but only for AMR microorganisms in c). AHI supports actions which work to reduce overall food borne microbial contamination of which antibiotic resistant bacteria are only a small fraction. The goal of minimizing food borne microbial contamination is consistent with the new Food Safety Initiative. Post-harvest interventions are generally more effective than on-farm interventions. AHI notes that only selected foods are included in objectives a), b) and c) and recommends to the Co-Chairs that interventions for all foods of animal origins be included; and potentially to crops. Finally, it should be noted that new product development and commercialization is more dependent on industry than on USDA.
- 3.6 c) – We were not aware that there is an Antimicrobial resistance problem in eggs or that there are specific interventions to reduce AR bacteria in egg processing?
- 3.7 AHI notes that these initiatives are not specific to antimicrobial resistant food borne microbes and supports education campaigns that promote safe food practices. Again, the support for post-harvest interventions is welcomed because it signals the key role as a critical control point that will contribute to decreasing not only antimicrobial resistant food borne pathogens, but all bacteria and pathogens and thereby improve food safety and public health. AHI notes that the accomplishment dates for all 3 objectives is since past, thus it is questionable as to why they appear in the Action Plan.
- 3.8 AHI supports educational programs for veterinarians and other food chain workers. However, AHI questions why curriculum is being developed exclusively by agencies instead of professional organizations? It seems that an inventory of existing guidelines and

recommendations is needed before engaging in a new initiative to ensure that the objective is duplicating existing materials.

Goal 4: Develop, implement, and evaluate strategies to improve appropriate antimicrobial use.

- 4.1 a) – Should this objective also be applied to animal health uses? Why is it not linked to other objectives that mention usage practices? There is no way to be certain that the objective is not redundant with others.
- 4.1 f) – This objective concerns the evaluation of benefits and unintended consequences for human use so why can't this also be done for veterinary antibiotic use? In the prior Action Plan, risk-benefit assessments were included for veterinary antibiotic uses; but are not included in this version. AHI views this inconsistency as inappropriate and strongly recommends that the Co-Chairs amend the Action Plan to include risk-benefit assessments for animal antibiotic use to guide the appropriate use strategies.
- 4.2 As mentioned previously, there are international guidelines available from WHO, OIE, and Codex that provide guidance to national authorities on the appropriate use of antimicrobials in animal health settings. The objectives in this section should align with them. AHI believes that the appropriate Coordinator for this section is FDA and CDC should be deleted.
- 4.2 a) – AHI is concerned about any expansion of the Guidance 152 categorization of antibiotics that is not focused primarily, if not exclusively, on foodborne pathogens.
- 4.2 b) – FDA CVM draft Guidance 209 is already issued. The objective should also mention the Advance Notice of Proposed Rule Making for VFD modernization.
- 4.3 c) – AHI believes that it is inappropriate for this recommendation to be made when it is an agency decision. The original order was revoked pending further review, which has not yet been made available.
- 4.3 d) – Objective d) seems more appropriately placed in the Surveillance section of the Action Plan, since there are no guidelines that are to be developed. As well, antimicrobial susceptibility testing methods are not available for the listed bacteria.

Page 24 - Focus Area III: Research

General goal provides no valuable information on what will be done, success metrics, or a timeline or how the research data will be connected to other goals. It is not clear whether any of the objectives listed will include opportunities for animal health product development. The Co-Chairs are encouraged to include animal health applications to the greatest extent possible.

Goal 8: Conduct and support epidemiological studies to identify key drivers of the emergence and spread of AR in various populations.

- 8.2 a) – It would seem appropriate to use NARMS data in the communication.
- 8.3 Sentinel human populations seems to be a prospective undertaking that would require enormous resources and be fraught with legal issues. The question of what to do with the information derived remains unanswered.
- 8.3 a) – These risk factors are already reasonably well known and understood, so why are more needed? What is in need of investigation is multi-drug resistant *S. typhi*, a human pathogen.
- 8.4 This is a huge administrative undertaking. It is not clear what value this would deliver.

Page 27 - Focus Area IV: Product Development

AHI seeks to include FDA/CVM, USDA and EPA for animal health products. Animal health especially needs to encourage innovation for non-medically important antimicrobials and non-antibiotic interventions for animal disease.

Goal 9: Provide information on the status of antibacterial drug product development and clarify recommended clinical trial designs for antibacterial products.

- 9.4 AHI encourages FDA to specifically include the new Innovation initiative in the FDA Center for Veterinary Medicine which is an industry-regulatory partnership that seeks to promote appropriate regulatory reviews of new technology.
- 9.5 MUMS should also be explored for development and marketing of new antimicrobials for veterinary medicine that fill unmet and critical animal health needs.
- 9.6 AHI would like to include animal health product development incentives in this objective.

Goal 10: Consider opportunities for international harmonization and means to update susceptibility testing information for human and animal use.

AHI notes that there are similar global organizations in the animal health sector for which similar harmonization opportunities exist. These include not only OIE and VICH, but Codex.

- 10.3 The process for updating susceptibility testing information, particularly those that result in breakpoint changes, requires a significant amount of data. It is unclear how the objective to develop a strategy will be accomplished, given that the sampling scheme for isolates is critical to the outcome. Other objectives in the document need to be related to this one to facilitate a coordinated outcome.
- 10.3 a) – AHI supports methods development for susceptibility testing of veterinary pathogens and notes that the CLSI Veterinary Antimicrobial Testing Subcommittee has been

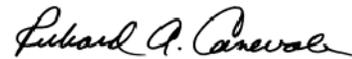
engaged in this work for some time. Participation by government personnel in the CLSI process is welcomed.

Goal 11: Encourage development of rapid diagnostic tests and vaccines.

AHI encourages the Co-Chairs to include support for veterinary diagnostics, vaccines, and other non-antibiotic approaches. This would be supportive of Responsible Use guidelines. As well, it is consistent with the One Health Initiative.

Thank you in advance for your consideration of these comments. Should you have any questions, please do not hesitate to contact AHI at (202) 637-2440.

Sincerely,

A handwritten signature in black ink that reads "Richard A. Carnevale". The signature is written in a cursive style with a large, stylized initial 'R'.

Richard A. Carnevale, VMD